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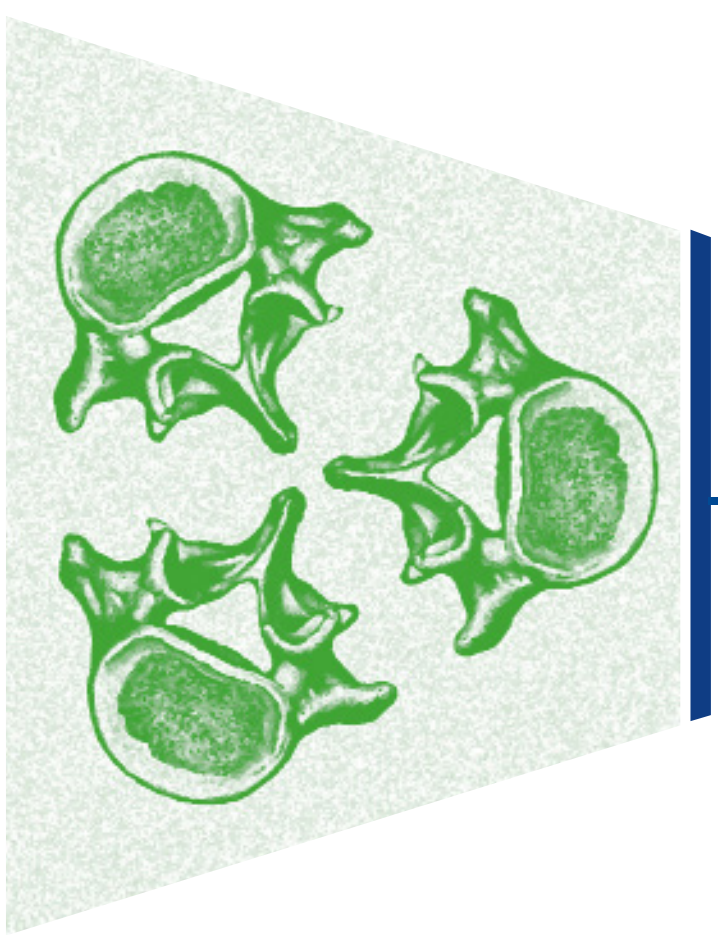

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RESEARCH ARTICLE

Access to healthcare as an important moderating variable for understanding the geography of COVID-19 outcomes – preliminary insights from Poland

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Abstract

Introduction: Biases in the measurement of COVID-19 burden and the uncertainty in estimation of the corresponding epidemiologic indexes are known and common phenomena in infectious diseases. We investigated to what extent healthcare access (HCA)-related supply/demand interfered with the registered data on COVID-19 in Poland. **Material and Methods:** We ran a multiple linear regression model with interactions to explain the geographic variation in seroprevalence, hospitalizations (on the voivodeship – NUTS-2 level) and current (beginning of the 4th wave of COVID cases – 15.09-21.11.2021) case notifications/crude mortality (on poviat – old NUTS-4 level). We took vaccination coverage and cumulative case notifications up to the so called 3rd wave as predictor variables and supply/demand (HCA) as moderating variables. **Results:** HCA with interacting terms (mainly demand) explained to the great extent the variance of current incidence and most of the variance in the current mortality rates. HCA (mainly supply) was significantly moderating cumulative case notifications until the 3rd wave of cases, thus explaining the variance in seroprevalence and hospitalization. **Conclusion:** Seeking causal relations between the vaccination- or infection-gained immunity level and the current infection dynamics could be misleading without understanding the socio-epidemiologic context such as the moderating role of HCA (sensu lato). After quantification, HCA could be incorporated into epidemiologic models for improved prediction of the actual disease burden.

Keywords: healthcare access · health inequalities · COVID-19 · statistical modelling · immunity level · quasi-causal diagrams

Citation

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TRANSPARENT PROCESS OPEN ACCESS

Introduction

From epidemiologic practice, we already know that registered disease case notifications do not reflect the actual burden of infections (including so called "dark figure") to the same extent in various geographic locations due to socio-economic-medical inequalities [1]. Therefore, healthcare access (HCA) has already been identified as a possible factor influencing measurable Coronavirus disease 2019 (COVID-19) epidemic indexes and explaining intra-country variation [2-5]. Thus, more resource-rich regions were able to organize both testing and treatment resources [6] and vaccination campaigns [7] in a faster and more inclusive way, whereas resource-poor regions were much more selective in the pandemic healthcare services delivery.

Epidemiological modeling and healthcare analytics

Knowing immunity levels is important for proper prediction of the COVID-19 dynamics for a given region. Researchers proposed multiple methods and models explaining acquiring natural immunity (possibly after infection) and vaccine-induced immunity, taking into account their interactions as well as various immunity waning schema [8-9]. We know quite well how the efficacy of various vaccines is waning over time [10] against symptomatic infections (controlled for covariates such as seasonality or virus variants), however post-infection immunity is much more difficult to assess [11]. Seroprevalence studies also can be used to estimate immunity levels and have previously been used extensively to estimate infection fatality rate (IFR) [12-13].

Modeling Paradoxes

To unravel the so-called "epidemiological mystery" of COVID-19 [14] it is currently attempted to identify the contextual factors associated with case and death reports with real infection and fatality rates. Researchers from Institute for Health Metrics and Evaluation [14] estimated that the cumulative number of unreported cases until the so-called 4th wave of COVID-19 varies significantly even among countries within close geographic proximity. Using Eastern Europe as an example ("dark figure" size), in Slovakia the number of reported cases should be increased by 13% in order to reflect the estimate of actual infection, in Poland by 517%, while in Russia by 2230%. This example published in The Lancet reveals the scale of the problem associated with reporting and understanding COVID-19 outcomes. Moreover, some recent ecological studies are suggesting a weak or no link between vaccination coverage and the current (Delta variant) epidemic dynamics in the general populations [15-16] as well as little to no effect of NPI (nonpharmaceutical interventions) on COVID-19 incidence and mortality [17-18]. Not surprisingly, these findings caused a wave of controversy and our observations put a new light on them.

HCA and modeling

Surprisingly, HCA has not yet been significantly addressed in the practice of infection dynamics modeling [5]. Although immunity is gained and lost at the individual level, it is often attempted to quantify the immunity level at a population level, for instance by accounting for biased measures such as estimates of undiagnosed cases or eliciting seroprevalence via surveys. Innacurate estimates of COVID-19 immunity levels varying across time and regions make predictions challenging and significantly reduce predictive power. Therefore, forecast results often deviate from reality, as was the case in Poland between June – September 2021 [19]. It is worth mentioning that the simple forecasting model "PL_GRedlarski-Districts-Sum" (created by a volunteer from the Medical University of Gdańsk) which sums up extrapolation of COVID-19 cases' trajectories in poviats (implicitly assuming their idiosyncrasy and heterogeneity driven by HCA among others) is overperforming in short- and medium-term all other models [20], including those that are financed and used by Polish Ministry of Health or ECDC. Albeit we could simply mechanistically mimic reporting patterns, we still do not know what are intra-country differences in shares of unreported cases. More or less accurate inter-country estimates in Eastern Europe (sharing the similar post-communist social and health care patterns) are showing variability greater than two orders of magnitude [14].

Our aim was to show on the example of Poland that omitting HCA confounding/moderating factors could lead to misinterpretation in understanding the current epidemic dynamics due to biased estimation of immunity levels and other epidemiologic indexes.

Material and methods

Data description

Data obtained from the registries of 16 voivodeships of Poland (Nomenclature of Territorial Units for Statistics, NUTS-2) and 380 poviats (old NUTS-4) only from publicly available official sources or their archived versions. For instance, historical hospitalization rates are not publicly available and only can be scrapped from the archives of governmental webpages. In our model we considered the variables listed below.

Independent variables:

- **Cumulative No, cases per capita:** The cumulative numbers of COVID-19 notifications until the so-called 3rd wave of epidemic (04.03.2020-15.06.2021) for poviats and voivodeships [21] divided by its population size.

- **Fraction of vaccinated:** Percentage of people vaccinated with at least one dose for poviats and voivodeships (at the end of 3rd wave at 15.06.2021) for all age groups [22]. Vaccination coverage gives us a proxy of proportions of population which gain post-vaccination immunity before the so-called 4th wave.

Moderating variables:

- **Healthcare Access – Supply (supply HCA):** The number of physicians working in health care per 10000 inhabitants in 2019 as an indicator of the HCA supply for poviat and voivodeship [23]. This is a good proxy for capacity and accessibility of healthcare (public and private).
- **Healthcare Access – Demand (demand HCA):** The number of consultations in primary care provided in 2019 for poviats and voivodeships as an indicator of the demand for HCA [23]. Pearson correlation between demand HCAs in 2019 and 2020 is 0.998 [7], so no significant regional changes have been observed in the demand for HCA due to the pandemic. Demand for HCA is a complex conglomerate of attitudes towards healthcare (i.e., level of trust in the effectiveness of treatment offered by public healthcare), perceptions of accessibility (i.e., how easily one can reach healthcare facilities), and disease burden (i.e., elderly and inferior health populations are more likely to seek for healthcare).

Dependent variables:

- **Normalized incidence Sep/Oct'21:** 2-week incidence of COVID-19 notifications (21.09–04.10.2021) during the beginning of the so-called 4th epidemic wave for a poviat [21].
- **Normalized deaths Sep/Nov'21:** Crude mortality rate – Cumulative number of COVID-19 death cases (15.09-21.11.2021) during the so-called 4th epidemic wave per poviat divided by its population size [24].
- **Normalized hospitalizations:** Number of occupied hospital beds (14.10.2021) at the beginning of the so-called 4th epidemic wave per voivodeship divided by its population size [25].
- **Obser-Co:** The fraction of seroconverted [26] per voivodeship in a random (by design) sample as a proxy for immunity level collected during 29.03-14.05.2021. This variable is a good proxy of post-infection acquired immunity as this time frame was the end of the 3rd epidemic wave and at the start of the vaccination roll-out was at the beginning.

The dynamics of the SARS-CoV-2 spread vary across the spatial clusters and initial conditions as the number of index cases and immunity levels could lead to different phases at the beginning of each wave. We chose the beginning of the 4th wave for epidemiologic indexes (dependent variables): hospitalizations and incidence due to relatively equal distribution of the Delta variants across country, when the wealthier part of population returns from vacation trips abroad [27], children return to school (September) but before the start of the new academic year in October (possible movement of population to large cities), in order to avoid some artefacts due to introduction or re-emergence of variants [6, 28]. For mortality rates, we decided to take a longer period (up to maximum in incidence of 4th wave), in order to gather enough data.

HCA access definition

Supply/demand HCA are assumed to be moderating variables that affect the relationship between the independent variables (vaccine or post-infection immunity at the end of the 3rd wave) and dependent variables (seroprevalence and the 4th wave outbreak outcomes).

Our bidimensional HCA measure is a combination of [5, 14, 29-33]:

- Regional healthcare capacity or quality (corresponding to supply HCA) which other researchers have sought to examine, such as Health Security Index, Universal Health Coverage Index, Healthcare Accessibility and Quality Index, Human Development Index, number of physicians or nurses per capita, number of hospital beds per capita, government and total health spending per capita, number of tests performed per capita, Cumulative Standardized Testability Ratio;
- Behavioral patterns of using healthcare related to population demographic or comorbidity structure (corresponding to demand HCA) which other researchers were trying to capture by age structure (e.g., share of seniors), BMI (e.g., share of obese), pulmonary or immunodeficiency diseases prevalence, number of medical consultations, share of smokers;
- The affective social conditions corresponding to the way how people are likely to seek healthcare services (corresponding to demand HCA) which other researchers have tried to capture by the prevalence of magical thinking (e.g. interests in alternative medicine), ethnic structure, political populism, income inequality (e.g. intra- or inter-regional Gini coefficient), trust (in medical professionals, government or science) and affective autonomy (the normative tendency for people to maximize their own utility).

Thus, our socio-medical concept of HCA is covering a wide range of complex constructs and the goal of this paper is to demonstrate its importance.

Regression models

We provide an empirical, rather than theoretical, approach for analyzing the links between the dependent and independent variables moderated by covariates (HCA).

The commonly used approach (though not the state of the art [34]) for assessing a causal model is a multiple regression analysis [35] with interactions between variables (moderating and independent). Multiple linear regression was proposed in 4 equations n∈{1,2,3,4} with 4 predictors consisting of i∈{1,2} independent and ∈{3,4} moderating variables:

$$Y_n(z) = \alpha^n + \sum_{i}^{4} \alpha_i{}^n X_i(z) + \sum_{i \neq j} \alpha_{ij}{}^n X_i(z) X_j(z)$$

Where generally: Y_n are dependent variables; X_1 and X_2 are independent variables; X_3 and X_4 are moderating variables, XiXj are 2- way interactions terms among the predictors.

Where specifically: Y_1 – seroprevalence – Obser-Co; Y_2 – Normalized Hospitalizations; Y_3 – Normalized incidence Sep/Oct'21; Y_4 – Normalized deaths Sep/Nov'21; z is one of 18 voivodships for Y_1 and Y_2 or one of 380 poviats for Y_3 and Y_4; X_1 – Cumulative No. cases per capita (independent variable); X_2 – Fraction of vaccinated (independent variable); X_3 – Healthcare Access – Supply/supply HCA (moderating variable); X_4 – Healthcare Access – Demand/demand HCA (moderating variable); α are intercepts (without subscript indices) and slope parameters (with subscript indices).

Flow of explained variance of each dependent Y_n variable (in %) by predictors X_i and interactions among them is drawn on diagrams (Fig. 3-6). Models at the level of each geographical unit (poviat and voivodeship) should be compared separately. Because there is a known geographical phenomenon that the use of larger spatial units (NUTS-2/3, voivodeships) results in a better adjustment of statistical models (higher explained variance), due to the aggregation (averaging) of data for these units [36]. Graphical representation of possible causation links on diagrams is an informal visualization tool in our case, but has a formal mathematical form [37] for instance in Structural Equation Modeling (SEM), Path Diagrams or Directed Acyclic Graphs (DAG). Our model does not formally recognize independent or moderating variables, so presentation of directionality of interactions terms on diagrams is convention only.

Results

Data exploration

Descriptive statistics of variables were analyzed. Clusters of correlated related variables can be noticed in a hierarchical arrangement of the correlation matrix and corresponding dendrograms (Fig. 1).

There is a very strong and significant (R = 0.74, p-V = 0.03) correlation between the demand for HCA and cumulative cases per capita (Fig. 1 Top). To remind, demand HCA was assessed before the pandemic started, thus geographic distribution of reported normalized cases aggregated over the first three waves is highly dependent on the structural patterns of how people tend to use healthcare. On the other hand, the supply of HCA is strongly correlated with the vaccination rate

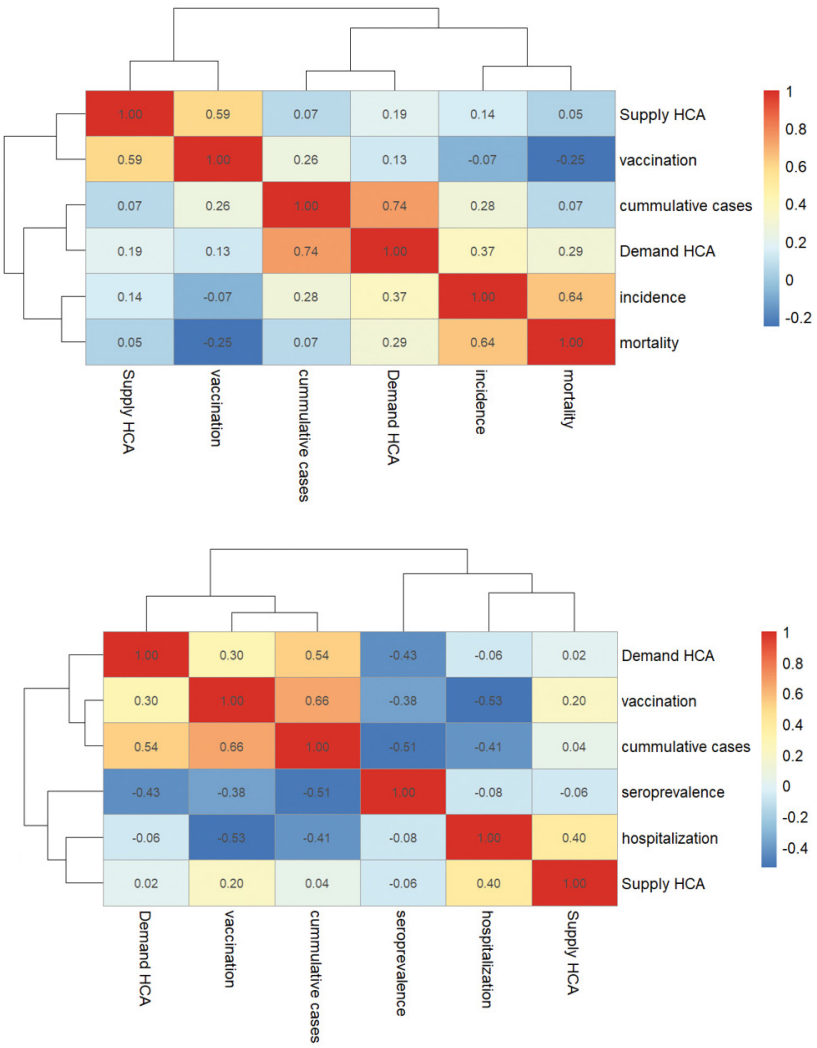

Figure 1. Pearson correlation matrix between the variables considered in the analysis in the hierarchical system. Dependent variables were considered at the poviat (Top) and voivodship (Bottom) levels. Independent and moderating variables available at the poviat level have been aggregated to the voivodeship level

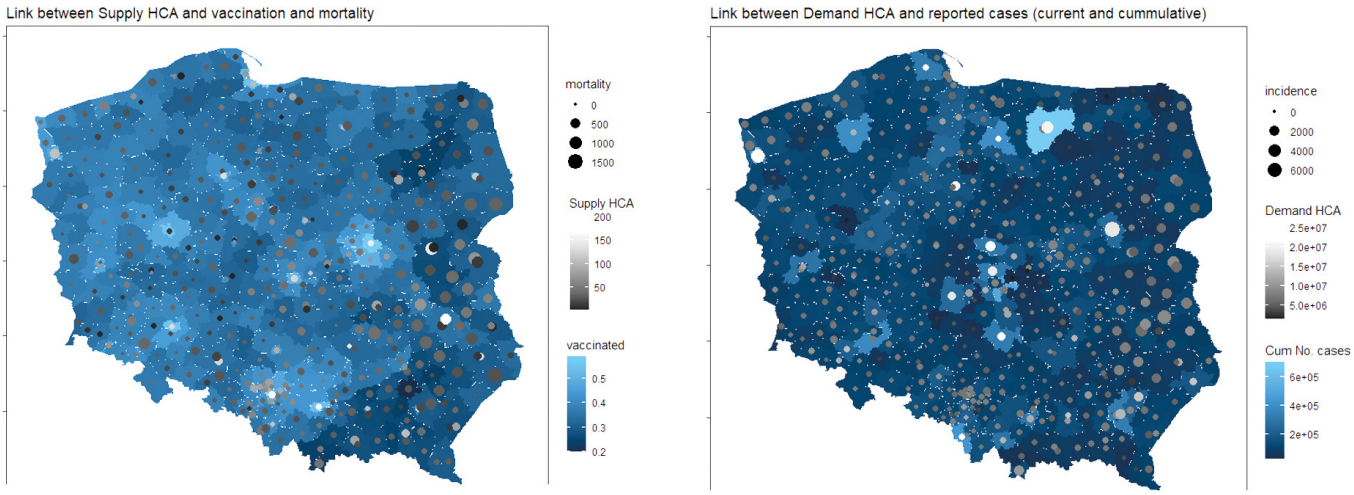

Figure 2. Map of the selected significant determinants of COVID-19 outcomes on poviat level. Left: with Supply HCA, Right: with demand HCA

(R = 0.59, p-V = 0.09). This could mean that the vaccination program was more popular in regions with higher healthcare capacity. On the voivodeship level (Fig. 1 Right) seroprevalence is significantly and negatively correlated with demand HCA (R = -0.43, p-V = 0.05) as well as negatively correlated with cumulative cases (R = -0.51, p-V = 0.06). It is important to note the paradox, that higher reported cumulative cases correspond to lower seroconversion rate, which can only be explained by the structural geographical biases (for instance, due to intra-voivodeship variation in the variables being compared or inter-voivodeship variation of undiagnosed cases). Unfortunately, hospitalization rates are not available on poviat level, so we choose to visualize geography of cumulative and current incidences mediated by demand HCA (Fig. 2 right) and vaccination rates and crude mortality moderated by supply HCA (Fig. 2 left).

Mapping (Fig. 2) shows that both moderating HCAs are highly granulated and do not cluster spatially to such extent as independent variables [6-7]. Thus, due to high heterogeneity within even close geographic neighborhoods (for instance between big cities and rural poviats), analysis on the level of voivodeship could be not sufficient.

Regression models

The following predictor variables were used: vaccination coverage, cumulative case notifications, conditions moderating supply/demand HCA as well as 2-way interactions among them (Tab. 1, Fig. 3-6).

The models presented in Table 1 were not selected according to statistical criteria. Therefore, there may be other models based on the same set of predicting variables with

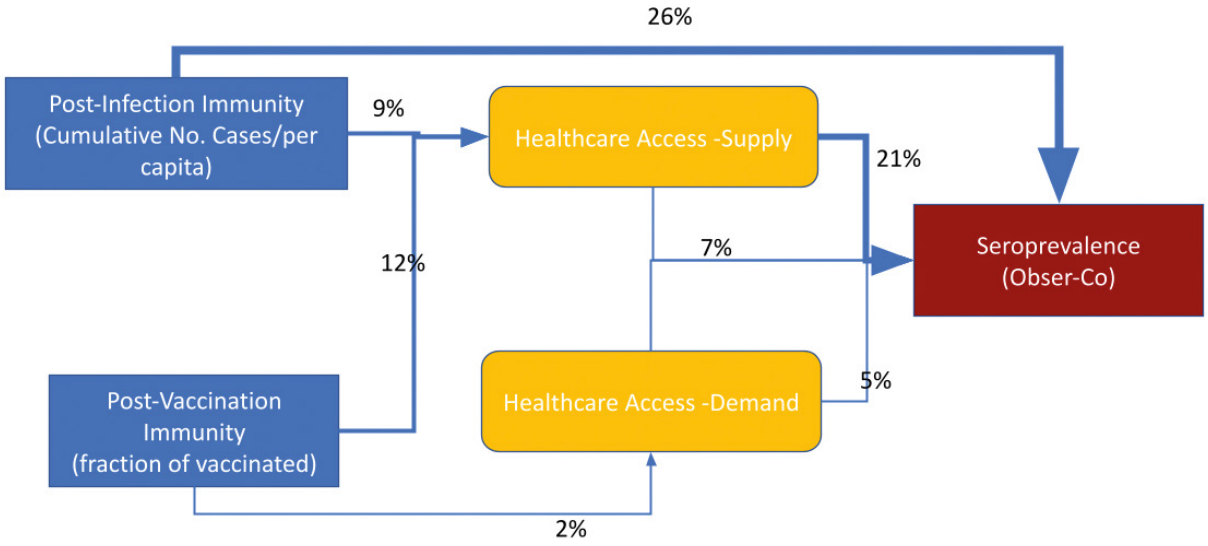

Figure 3. Explained variance of seroprevalence at the end of 3rd wave – immunity level estimation from Obser-Co [26] on voivodeship level

a better fit. However, these simple regressions allow us to highlight which variables and which interactions need further investigation. More variance is explained for hospitalizations (82%) than seroprevalence (61%) on the voivodeship level. More variance is explained for deaths (25%) than incidence (23%) on the poviat level. In a series of diagrams, we depict the explained share of variance for selected dependent variables of interest as calculated by multiple regression.

HCA (mainly supply indirectly) is significantly influencing seroprevalence survey results (Fig. 3). Thus, 9% of variance is explained by the interaction between cumulative case notifications and supply HCA. It's worth mentioning that demand HCA is even significantly correlated with seroprevalence surveys (see Fig. 1 Top), which has not been replicated in the regression model (only 3% of explained variance directly). Most of the variance in seroprevalence is explained directly (26%) by cumulative cases notifications. Vaccination was in a very early stage at the time of the seroprevalence survey, however there is an interaction pattern between supply HCA and vaccination (12%).

Hospitalizations seem to be well predicted by vaccination coverage and cumulative cases notifications (47% of variance considering also the interaction between them). HCA (mainly supply) affects hospitalizations (Fig. 4), but 12% of variance is explained by the interaction between vaccination coverage and supply HCA.

HCA (mainly demand) is extremely important (Fig. 5-6) to predict current infections dynamic (incidence and mortality). It is worth stressing that the direct links between vaccination coverage as well as cumulative case notifications with current incidence are statistically negligible (only the interactions with these terms have some impact).

Table 1. Percentage of explained variance (%Exp) and significance level (p-V) for dependent variables (red) for given selection of predictors with interactions as independent variables (blue) or moderating variables (yellow)

dependent variable	Seroprevalence		Hospitalizations		Incidence*		Deaths	
predictor	p-V	% Exp	p-V	% Exp	p-V	% Exp	p-V	%Exp
cumulative cases	0.129	26	0.022	17	0.480	0	0.112	1
fraction of vaccinated	0.840	0	0.017	20	0.129	0	< 0.001	9
supply HCA	0.889	0	0.022	17	<0.001	3	0.375	0
demand HCA	0.543	3	0.191	4	<0.001	15	< 0.001	13
cumulative cases: supply HCA	0.330	9	0.719	0	0.006	1	0.172	0
cumulative cases: demand HCA	0.976	0	0.564	1	0.594	0	0.875	0
cumulative cases: fraction of vaccinated	0.900	0	0.027	15	0.003	3	0.012	1
demand HCA: fraction of vaccinated	0.611	2	0.549	1	0.016	1	0.007	1
supply HCA: fraction of vaccinated	0.266	12	0.038	12	0.461	0	0.364	0
supply HCA: demand HCA	0.393	7	0.118	6	0.068	1	0.336	0
Residuals	-	39	-	18	-	77	-	75

* Incidence is sensitive to quadratic as well 3rd way interaction terms, thus it will need further robustness analysis.

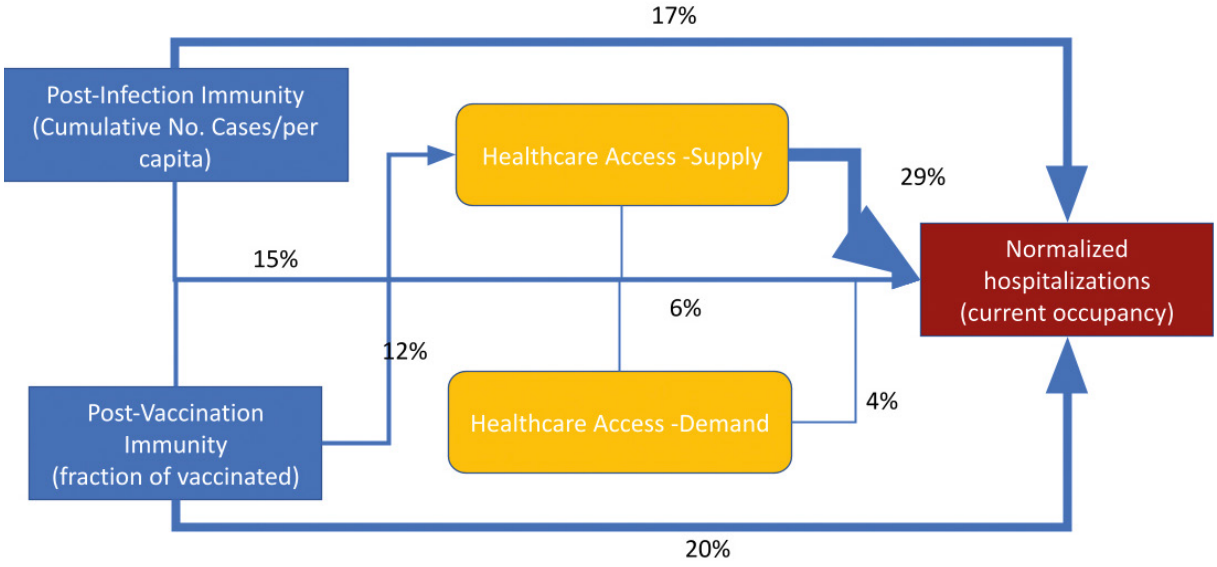

Figure 4. Explained variance of hospitalizations during the 4th wave on the voivodeship level

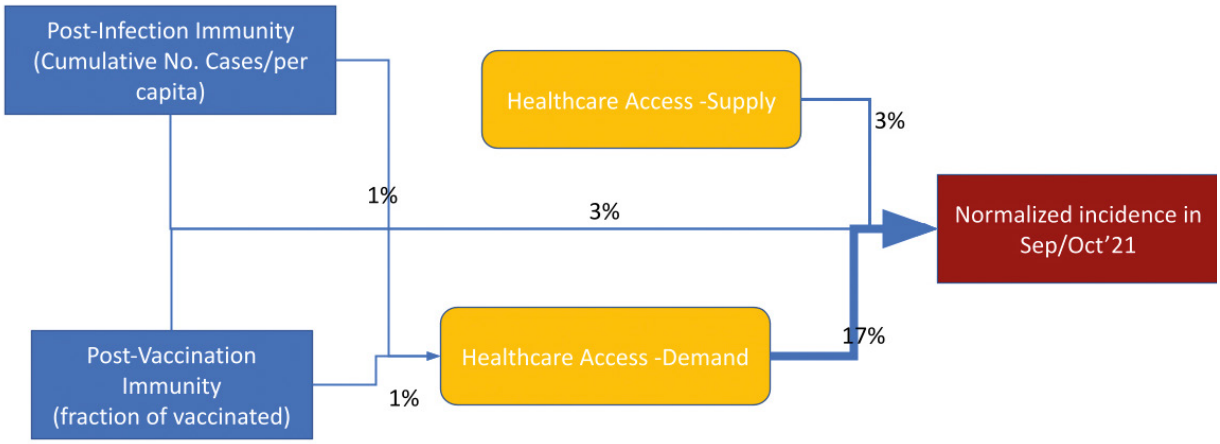

Figure 5. Explained variance of normalized case notifications (14-days incidence) during the 4th wave on the poviat level

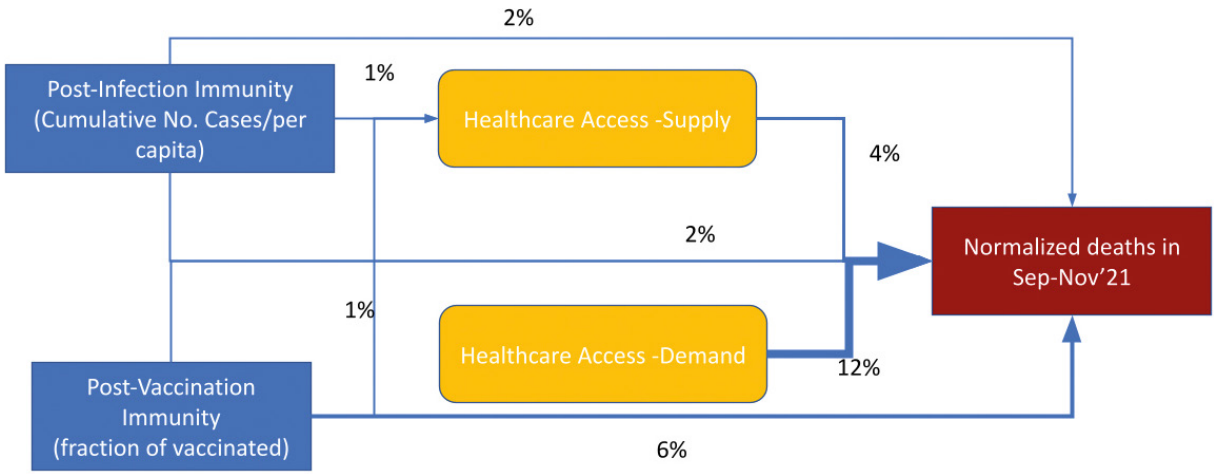

Figure 6. Explained variance of crude mortality rate during the 4th wave on the poviat level

Crude mortality rate (Fig. 6) in comparison to incidence (Fig. 5) during the beginning of the 4th wave is less prone to the confounding effect of HCA. We can see a significant link between vaccination coverage and crude mortality rate due to COVID-19 (Fig. 6).

Discussion

Discussion of regressions

There are multiple possible mechanisms explaining mediating role of HCA (however causal statements cannot be defined as probably both explaining and explanatory variable seems to depend on HCA):

- In regions with high healthcare service/worker availability (supply HCA) patients are more likely to be sampled as seroconverted (Fig. 3), have a higher chance of finding a hospital bed (Fig. 4), as well as higher chance of being tested (and get a positive result) (Fig. 5).
- Case notifications, as well as in some extent crude mortality (Fig. 5, 6) are highly correlated with the way patients are likely to use the public healthcare system (demand HCA), thus in regions with low demand HCA the real number of infections seems to be underestimated by documented case notifications to a higher extent than in places with high demand HCA.

We found that hospitalizations seem to be the most understandable for a given set of predictor variables (the highest variance explained and potentially strong model robustness) as well the least dependent on HCA (Tab. 1, Fig. 4). On the other hand, incidence is the most difficult to assess and interpret (the lowest variance explained and weak model robustness) as well as the most prone to be driven by HCA (Tab. 1, Fig. 5).

Modeling paradoxes and interpretation

Each epidemiological index is more or less confounded by HCA in different ways: seroprevalence obtained via surveys and hospitalizations mainly by supply HCA, but documented case notifications and crude mortality rates mainly by demand HCA. All of the investigated epidemiologic indexes (Tab. 1) are highly dependent on HCA within a single country with similar surveillance methodology across regions (at least in theory). Therefore, inter-country comparison or measuring effectiveness of vaccination or NPIs for a selected index lead to possible biases in interpretation [14, 16-18] even unintentionally. As we found that that reported geographic variability of incidence is more prone to be driven by the socio-epidemiological factors rather than the dynamic infectious process, all of the ecological analysis using this outcome must be interpreted with extreme caution. Moreover, the lack of or even slightly positive correlations between the reported incidence (during the 3rd and 4th wave) and the vaccination rates by regions was confirmed in our study as significantly confounded by HCA (Fig. 5). As this argument is often used by the so-called anti-vaccination and anti-sanitarian movements, it is worth mentioning that causal relation cannot be claimed with the observed moderating role of HCA (possibly due to bias in the tendency of seeking available healthcare in the mild course of the disease). Thus, vaccination was not only averting hospitalizations [25] or death tolls [38] in Poland (Fig. 4, 6), but also probably has reduced transmission probability (at least until the introduction of the Omicron variant), although it may be partially masked by inequalities in HCA (Tab. 1, Fig. 5).

Limitations and future work

It's important to mention that regression with incidence as an independent variable is the least robust (sensitive to adding 3-way interaction terms as well nonlinear forms of dependent variables), however this is out of scope of this preliminary work. This study is only an exploratory, so-called "zero" approach to illustrate the mediating phenomenon due HCA differences between geographical regions. Our approach has multiple limitations because vaccination coverage, cumulative case notifications, seroprevalence and current outbreak dynamics are snapshots from a given time point and were considered for different time periods. Due to availability of explained variables on different levels (voivodeship or poviat) model comparison should be done with caution. Other possible interfering variables were not taken into consideration (such as socio-economic-demographic portrait of the population) and other studies found that HCA could be collinear with multiple variables [39]. Further causal modeling using a longitudinal approach is required to support our preliminary observations. These results are specific to the Polish population/healthcare system and the role of the HCA could be different in other settings.

Conclusions

Recommendation

The moderating roles of HCA could change over time. However, this simple analysis suggests that including HCA indexes into models of disease dynamics will increase their short-term (meteorological conditions could be added as well [40]) and could increase long-term predictive power. Only triangulated pictures based on reported cases (with estimates of undiagnosed infections), deaths (due to COVID-19 and excess mortality), and hospitalizations (separately with and due to COVID-19), may allow for epidemiological interpretation. Thus, there are mathematical approaches of

reducing the bias by combining multiple epidemiological indexes or constituting their derivatives [41-42]. For instance, crude fatality rates [43] seem to be less dependent on HCA than estimates of IFR in Poland. Moreover, recent suggestions of ECDC [44] and WHO [45] to put more emphasis on hospitalizations/mortality rather than laboratory confirmed cases in understanding the burden of disease are also supported by our findings. We regret that data gathered by state is not provided in an easy to analyze format [46] and a massive manual work is needed for data preparation. The most important and probably the least biased variable (according to our preliminary analysis) – hospitalization (being a good proxy for the severe cases) – is not available on poviat level (old NUTS-4) in Poland. We suggest that the number of hospitalized patients originating from a given region (poviat or even municipality) could be a very significant epidemiologic index.

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Conflicts of interest

None.

References

1. WHO. Handbook on health inequality monitoring: with a special focus on low- and middle-income countries. World Health Organization; 2014.
2. Sun Y, Hu X, Xie J. Spatial inequalities of COVID-19 mortality rate in relation to socioeconomic and environmental factors across England. Sci Total Environ [Internet]. 2021 Mar;758:143595. Available from: https://www.sciencedirect.com/science/article/pii/S0048969720371266
3. Dahal S, Luo R, Swahn MH, Chowell G. Geospatial Variability in Excess Death Rates during the COVID-19 Pandemic in Mexico: Examining Socio Demographic and Population Health Characteristics. medRxiv [Internet]. 2021 Jan 1;2021.08.11.21261930. Available from: http://medrxiv.org/content/early/2021/08/12/2021.08.11.21261930.abstract
4. Andersen LM, Harden SR, Sugg MM, Runkle JD, Lundquist TE. Analyzing the spatial determinants of local Covid-19 transmission in the United States. Sci Total Environ. 2021;754:142396.
5. Ayoub HH, Mumtaz GR, Seedat S, Makhoul M, Chemaitelly H, Abu-Raddad LJ. Estimates of global SARS-CoV-2 infection exposure, infection morbidity, and infection mortality rates in 2020. Glob Epidemiol. 2021;3:100068.
6. Jarynowski A, Wójta-Kempa M, Krzowski Ł. An attempt to optimize human resources allocation based on spatial diversity of COVID-19 cases in Poland. medRxiv [Internet]. 2020 Jan 1;2020.10.14.20090985. Available from: https://www.medrxiv.org/content/10.1101/2020.10.14.20090985v1
7. Jarynowski A. Zróżnicowanie geograficzne szczepień p/COVID-19 w Polsce – nierówności społeczne i peryferyjność, a możliwe środki zaradcze [Polish] [Internet]. Academia. [cited 2022 Aug 30]. Available from: https://www.academia.edu/50340205/Zróżnicowanie_geograficzne_szczepień_p_COVID_19_w_Polsce_nierówności_społeczne_i_peryferyjność_a_możliwe_środki_zaradcze
8. Shearer F. Incorporating vaccine and exposure-acquired immunity into COVID-19 situational assessment [Internet]. The Fields Institute for Research in Mathematical Sciences. 2021 [cited 2022 Aug 30]. Available from: http://www.fields.utoronto.ca/activities/21-22/modelling-immunity
9. Glasser J. Calculating quantities needed for transmission modeling from large-scale serological surveys of antibodies to SARS-CoV-2 in the United States [Internet]. The Fields Institute for Research in Mathematical Sciences. 2021 [cited 2022 Aug 30]. Available from: http://www.fields.utoronto.ca/talks/Calculating-quantities-needed-transmission-modeling-large-scale-serological-surveys-antibodies
10. Nordström P, Ballin M, Nordström A. Effectiveness of Covid-19 vaccination against risk of symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study. Hosp Death Up to [Internet]. 2021;9(preprint). Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3949410
11. Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity [Internet]. CDC. 2021 [cited 2022 Aug 30]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html
12. Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. Eur J Clin Invest [Internet]. 2021 May 9;51(5):e13554. Available from: https://doi.org/10.1111/eci.13554

13. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. Int J Infect Dis [Internet]. 2020 Dec;101:138–48. Available from: https://www.sciencedirect.com/science/article/pii/S1201971220321809
14. Bollyky TJ, Hulland EN, Barber RM, Collins JK, Kiernan S, Moses M, et al. Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021. Lancet [Internet]. 2022;399(10334):1489–512. Available from: https://www.sciencedirect.com/science/article/pii/S0140673622001726
15. Subramanian S V, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States. Eur J Epidemiol [Internet]. 2021;36(12):1237–40. Available from: https://doi.org/10.1007/s10654-021-00808-7
16. Sobolewski M. Obraz statystyczny polityki zdrowotnej-analiza skuteczności szczepień przeciwko SARS-CoV-2 w zapobieganiu transmisji wirusa. Sympozjum „Oblicza pandemii" [in Polish] [Internet]. The College of Social and Media Culture in Toruń; 2022. Available from: https://www.youtube.com/watch?v=NbxX-yD4oRc&ab_channel=RadioMaryja
17. Herby J, Jonung L, Hanke SH. A literature review and meta-analysis of the effects of lockdowns on COVID-19 Mortality. Stud Aplied Econ [Internet]. 2022;(200). Available from: http://trudeauknows.ca/wp-content/uploads/2022/03/A-Literature-Review-and-Meta-Analysis-of-the-Effects-of-Lockdowns-on-COVID-19-Mortality.pdf
18. Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ [Internet]. 2021 Nov 18;375:e068302. Available from: http://www.bmj.com/content/375/bmj-2021-068302.abstract
19. European Covid-19 Forecast Hub. Forecasts · Cases, Poland; (June-September 2021) [Internet]. [cited 2022 Nov 1]. Available from: https://covid19forecasthub.eu/visualisation.html?fbclid=IwAR1dT9Qqb6nK9JLVipZsy6zqyrVg6LTPR5ndnT-gi-xDUSB1rSzXg2eNk2So
20. European Covid-19 Forecast Hub. Forecast scores, Poland [Internet]. 2022 [cited 2022 Aug 30]. Available from: https://covid19forecasthub.eu/reports.html
21. Rogalski M. Covid-19 wedlug powiatów [in Polish] [Internet]. 2020. Available from: https://docs.google.com/spreadsheets/d/1Tv6jKMUYdK6ws6SxxAsHVxZbglZfisC8x_HZ1jacmBM/edit?usp=sharing
22. Szczepienia w gminach [in Polish] [Internet]. Serwis Rzeczpospolitej Polskiej. 2022 [cited 2022 Aug 31]. Available from: https://www.gov.pl/web/szczepienia-gmin#/poziomwyszczepienia
23. Bank danych lokalnych [in Polish] [Internet]. Główny Urząd Statystyczny. 2020 [cited 2022 Aug 31]. Available from: https://bdl.stat.gov.pl/BDL/start
24. Statystyki zgonów z powodu COVID-19 [in Polish] [Internet]. Ministerstwo Zdrowia, Baza Analiz Systemowych i Wdrożeniowych. 2022. Available from: https://basiw.mz.gov.pl/index.html#/visualization?id=3653
25. Raport dobowy COVID-19 [in Polish] [Internet]. Ministerstwo Zdrowia. 2021 [cited 2022 Aug 31]. Available from: https://www.gov.pl/web/koronawirus/wykaz-zarazen-koronawirusem-sars-cov-2
26. Ogólnopolskie Badanie Seroepidemiologiczne COVID-19 – OBSER-CO: raport z I tury badania [in Polish] [Internet]. Narodowy Instytut Zdrowia Publicznego-Państwowy Instytut Badawczy. [cited 2022 Aug 31]. Available from: https://www.pzh.gov.pl/projekty-i-programy/obserco/raporty/
27. Śleszyński PA. Stages of spatial dispersion of the COVID-19 epidemic in Poland in the first six months (4 March-20 September, 2020) . [Internet]. Vol. 94. Warszawa: IGiPZ PAN; 2021. p. 305–24. Available from: http://rcin.org.pl/igipz/Content/211577/PDF/WA51_245709_r2021-t94-no3_G-Polonica-Sleszynsk.pdf
28. Jarynowski A, Wójta-Kempa M, Płatek D, Czopek K. Attempt to Understand Public Health Relevant Social Dimensions of COVID-19 Outbreak in Poland. SSRN Electron J [Internet]. 2020;4(3):7–44. Available from: https://www.ssrn.com/abstract=3570609
29. Jarynowski A, Wójta-Kempa M, Płatek D, Belik V. Social values are significant factors in control of covid-19 pandemic–preliminary results. Preprints.org [Internet]. 2020; Available from: https://www.preprints.org/manuscript/202005.0036/v1
30. Bosancianu CM, Dionne KY, Hilbig H, Humphreys M, Sampada KC, Lieber N, et al. Political and social correlates of covid-19 mortality. SocArXiv Pap [Internet]. 2020; Available from: https://osf.io/preprints/socarxiv/ub3zd/
31. Messner W, Payson SE. Contextual factors and the COVID-19 outbreak rate across U.S. counties in its initial phase. Heal Sci Reports [Internet]. 2021 Mar 2;4(1). Available from: https://onlinelibrary.wiley.com/doi/10.1002/hsr2.242
32. Parysek JJ, Mierzejewska L. Spatio-temporal analysis of the development of the COVID-19 epidemic (pandemic) in Poland: First phase of development. Geogr Pol [Internet]. 2021;94(3):325–54. Available from: https://rcin.org.pl/igipz/dlibra/publication/edition/211578
33. Migała-Warchoł A, Sobolewski M. The influence of the economic situation on the socio-economic development in the European Union countries by means of the modified HDI Index. Technol Transf Innov Solut Soc Sci Humanit [Internet]. 2020 Apr 30;3:28–31. Available from: http://journal.eu-jr.eu/ttissh/article/view/1485

34. Jonassen DH, Ionas IG. Designing effective supports for causal reasoning. Educ Technol Res Dev [Internet]. 2008;56(3):287–308. Available from: https://link.springer.com/article/10.1007/s11423-006-9021-6
35. Galea S, Hernán MA. Win-Win: Reconciling Social Epidemiology and Causal Inference. Am J Epidemiol [Internet]. 2020 Mar 2;189(3):167–70. Available from: https://doi.org/10.1093/aje/kwz158
36. Fotheringham AS, Wong DWS. The Modifiable Areal Unit Problem in Multivariate Statistical Analysis. Environ Plan A Econ Sp [Internet]. 1991 Jul 1;23(7):1025–44. Available from: https://doi.org/10.1068/a231025
37. Glymour MM, Greenland S. Causal diagrams. Mod Epidemiol [Internet]. 2008;3:183–209. Available from: https://publicifsv.sund.ku.dk/~jhp/KandidatFSV/aar19/Forelaesninger/DAG/GlymourChap12.pdf
38. Meslé MMI, Brown J, Mook P, Hagan J, Pastore R, Bundle N, et al. Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021. Eurosurveillance. 2021;26(47):2101021.
39. Kowalski PA, Szwagrzyk M, Kielpinska J, Konior A, Kusy M. Numerical analysis of factors, pace and intensity of the corona virus (COVID-19) epidemic in Poland. Ecol Inform [Internet]. 2021;63:101284. Available from: https://www.sciencedirect.com/science/article/pii/S1574954121000753
40. Bochenek B, Jankowski M, Gruszczynska M, Jaczewski A, Ziemianski M, Pyrc R, et al. Weather as a potential cause of regional differences in the dynamics of the COVID-19 epidemic in Poland - implications for epidemic forecasting. Polish Arch Intern Med [Internet]. 2021 Oct 8; Available from: https://www.mp.pl/paim/issue/article/16110
41. Kostoulas P, Meletis E, Pateras K, Eusebi P, Kostoulas T, Furuya-Kanamori L, et al. The epidemic volatility index, a novel early warning tool for identifying new waves in an epidemic. Sci Rep [Internet]. 2021;11(1):23775. Available from: https://doi.org/10.1038/s41598-021-02622-3
42. Michalak MP, Cordes J, Kulawik A, Sitek S, Pytel S, Zuzańska-Żyśko E, et al. Reducing bias in risk indices for COVID-19. Geospat Health [Internet]. 2022 Jan 14;17(s1). Available from: https://geospatialhealth.net/index.php/gh/article/view/1013
43. Gogolewski K, Miasojedow B, Sadkowska-Todys M, Stepień M, Demkow U, Lech A, et al. Data-driven case fatality rate estimation for the primary lineage of SARS-CoV-2 in Poland. Methods [Internet]. 2022;203:584–93. Available from: https://www.sciencedirect.com/science/article/pii/S1046202322000123
44. COVID-19 surveillance guidance - Transition from COVID-19 emergency surveillance to routine surveillance of respiratory pathogens [Internet]. European Centre for Disease Prevention and Control. 2021 [cited 2022 Aug 31]. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-surveillance-guidance
45. Guidance for surveillance of SARS-CoV-2 variants: Interim guidance [Internet]. World Health Organization. 2021 [cited 2022 Aug 31]. Available from: https://www.who.int/publications/i/item/WHO_2019-nCoV_surveillance_variants
46. Szmuda T, Ali S, Özdemir C, Syed MT, Singh A, Hetzger TV, et al. Datasets and future research suggestions concerning the novel Coronavirus (COVID-19). Eur J Transl Clin Med [Internet]. 2020 Dec 3;3(2):80–5. Available from: https://ejtcm.gumed.edu.pl/articles/72

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RESEARCH ARTICLE

Periprocedural decrease in tumor necrosis factor alpha is a risk factor for atrial fibrillation recurrence after ablation

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Abstract

Background: Concentration of tumor necrosis factor alpha (TNF-alpha) might be useful in selecting patients with paroxysmal atrial fibrillation (PAF) who will benefit the most from pulmonary vein isolation. **Material and methods:** This is a prospective cohort study among patients with PAF who had sinus rhythm prior to undergoing either radiofrequency ablation or cryoablation procedure. Blood samples were collected at the start of the procedure and 16-24 h after. TNF-alpha concentrations were measured. Follow-up data was obtained during a structured telephone interview and 24-hour ECG Holter monitoring 12 months after the ablation procedure. **Results:** Thirty seven patients were enrolled. After 12-month follow-up 27 patients maintained sinus rhythm, 8 had recurrence of AF and 2 were lost to follow-up. There was no significant correlation between TNF-alpha concentrations in any of the samples and the recurrence of arrhythmia (for pre-procedural samples: 1.75 pg/ml vs. 1.74 pg/ml; p = 0.72; for post-procedural samples: 1.49 pg/ml vs. 1.79 pg/ml; p = 0.16). In patients who had a recurrence of AF, we observed a decrease in the periprocedural TNF-alpha concentration (-0.12 pg/ml vs 0.05 pg/ml; p = 0.05). **Conclusions:** Neither pre- nor post-procedural TNF-alpha concentrations are predictive of ablation outcome in patients with PAF. We observed a decrease in the periprocedural TNF-alpha concentration in patients who had AF recurrence.

Keywords: subcutenous cardioverter-defibrillator (S-ICD) · ventricular pacing · sudden cardiac death

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Background

It is estimated that up to 2% of the population suffers from atrial fibrillation (AF) [1]. Mechanisms contributing to the development of AF remain to be fully discovered. Currently, it is believed that electrical and structural remodeling, changes in atrial cardiomyocytes and inflammatory processes play a pivotal role in initiation and perpetuation of AF [1-2]. The role of inflammatory cytokines deserves special attention, among which TNF-alpha needs further investigation. This molecule is synthesized mainly by monocytes and macrophages which infiltrate tissues during inflammatory processes, e.g. as a response to injury [3]. Immunologically active monocytes/macrophages infiltrate the atrial midmyocardium more extensively in patients with AF compared to those with sinus rhythm [4]. Animal models of TNF-alpha overexpression in the heart reveal a predisposition to atrial arrhythmias such as premature atrial beats, atrial flutter and AF, as well as increased collagen deposition [5]. Injection of TNF-alpha into Swiss albino mice leads to atrial fibrosis and altered connexin-40 expression [6]. In vitro studies have shown that TNF-alpha can increase the arrythmogenicity of pulmonary vein cardiomyocytes and influence cellular calcium homeostasis [7].

We hypothesized that the inflammatory reaction to atrial tissue damage measured by the change in TNF-alpha concentration could predict pulmonary vein isolation (PVI) outcome. The aim of our study was to compare TNF-alpha concentrations pre- and post-procedurally in patients who underwent pulmonary vein isolation due to paroxysmal AF (PAF) with and without recurrence of arrhythmia.

Material and Methods

We performed a prospective cohort study among patients with PAF undergoing radiofrequency (RF) ablation or cryoablation. PAF was defined according to the current ESC guidelines [1]. Patients who underwent the ablation procedure in the past were disqualified from the study. The protocol of the study was approved by the local ethics committee (ID: KB 46/2011). Informed written consent was obtained from each patient.

Exclusion criteria included any disease that is known to influence the TNF-alpha concentration, including heart failure (Table 1). Patients were also excluded from the analysis if AF was the initial rhythm observed at the beginning of the ablation procedure. Blood samples from a peripheral vein were obtained from each participant twice: before insertion of the ablation catheter into the vessel at the beginning of the ablation procedure and 16-24 h after. The blood was then centrifuged, serum was stored in -70°C. TNF-alpha levels were measured by high-sensitivity ELISA kit (R&D, Human TNF-alpha Quantikine HS ELISA Kit). Concentration > 30 pg/ml was recognized as an extreme value and excluded from the analysis according to the Tukey principles. Analyzed values included pre-procedural, post-procedural TNF-alpha concentration and the assessment of its periprocedural dynamics. Periprocedural TNF-alpha serum variations

Table 1. Exclusion criteria

Heart failure
Symptoms of inflammation during the clinical examination (e.g. signs or symptoms of pneumonia, urinary tract infection, dysuria, productive cough, skin ulceration)
History of myocardial infarction, stroke, burn wound, frostbite, major trauma or surgery within the past 30 days
History of autoimmune disease or vasculitis
Cirrhosis with ascites
Primary hyperaldosteronism, pheochromocytoma
Chronic kidney disease
Subarachnoid hemorrhage
Sarcoidosis, amyloidosis, hemochromatosis
Cardiac neoplasms
History of purulent dermatitis within the past 14 days

were calculated as a subtraction between post-procedural and pre-procedural TNF-alpha concentrations. The inflammatory response is dynamic only in the early post-ablation period, therefore we did not analyze TNF-alpha concentration during hospitalization.

Table 2. Baseline characteristics of the study population

	Study group (n = 37)
Age (years)	55.7 (SD 7.85)
Sex (male)	59.5%
Body Mass Index (kg/m²)	28.42 (SD 4.18)
Median time from diagnosis (months)	36 (IQR 19-108)
Median atrial fibrillation episodes frequency (per month)	1 (IQR 0.33-5)
Median duration of arrhythmia episode (hours)	8 (IQR 3-24)
Symptoms	97.3% (n = 36)
• heart palpitations	86.5%
• exercise intolerance	56.8%
• fatigue	51.3%
• hyperhidrosis	43.3%
• dyspnea	18.9%
Hypertension	54.1% (n = 20)
Diabetes	5.4% (n = 2)
Dyslipidemia	64.7% (n = 24)
Left atrium appendage diameter (cm)	4.26 (SD ± 0.54)
Left atrium systole surface (cm²)	17.16 (SD ± 4.04)
Left atrium diastole surface (cm²)	23.65 (SD ± 5.23)

All the patients had 24-hour Holter electrocardiograph (ECG) monitoring performed at least 4 times per year and were instructed to perform an ECG in case of palpitations. AF recurrence was defined as AF episode lasting > 30 seconds registered by the 3-lead 24-hour Holter ECG. The guidelines recognize 24-hour Holter ECG monitoring as a follow-up method. We are aware that the longer the tachycardia is monitored, the more often silent (asymptomatic) AF is detected. However, at present the goal of ablation is to improve the quality of life, not to eliminate atrial arrhythmia. In this approach, the main focus was on symptomatic AF. Follow-up data was obtained during a structured telephone interview 12 months after the ablation procedure, focused on identifying episodes of AF recurrence.

Statystical analysis

SAS 9.3 (SAS Institute, Cary, USA) was used for statistical analysis. All variables were tested for a normal distribution with the Shapiro-Wilk test. Normally distributed continuous variables are represented as mean ± standard deviation (SD) and nonnormally distributed continuous variables are represented as median [25th-75th percentile (IQR)]. Categorical variables are presented as number (percentage). Statistical comparisons for normally distributed continuous variables were performed with the Student t-test. TNF-alpha concentrations were not normally distributed, therefore Wilcoxon test was performed to compare the concentrations between patients with recurrence of AF and successful ablation as well as between the pre- and post-procedural samples. Statistical comparisons for categorical variables were performed with the $\chi 2$ test. Spearman's rank correlation coefficient was used to calculate the correlations.

Results

Study population

Out of 82 patients with PAF qualified for their first-time ablation procedure, 37 patients met the inclusion criteria and were enrolled in the study [22 male (59.5%),15 female; mean age 55.7 ± 7.85 years]. The median time since diagnosis of AF was 36 months (IQR 19-108 months), the median duration of AF episodes was 8 hours (IQR 3-24 hours) with the median AF episode frequency of 1 per month (IQR 0.33-5 per month). Baseline characteristics of the study population are shown in the Table 2. The most common concomitant diseases were hypertension (54%) and dyslipidemia (65%).

Twenty one patients underwent RF ablation whereas 16 patients underwent balloon cryoablation with the median duration of the ablation procedure of 2.5 hours. Detailed periprocedural data are shown in Table 3. A successful PVI was achieved in all patients. At the time of

Table 3. Periprocedural characteristics of study cohort

	Study group	Type of procedure	
		RF ablation	Cryoablation
Number of patients	37	21 (57%)	16 (43%)
Duration of procedure (hours)	2.5 (IQR 2.1-3.2)	2.42	2.58
Number of applications	22 (IQR 11.5-34)	30	11.5
Duration of applications (minutes)	45.7 (IQR 31-67)	33.1	63.8
Heart rate at discharge (beats per minute)	73 (SD ± 11)	75	71

RF – radiofrequency

discharge from the hospital, 34 patients had sinus rhythm (SR). During 12-month follow-up period 27 patients maintained stable SR, whereas 8 had recurrence of AF. Two patients were lost to follow-up.

Serum samples analysis

The median TNF-alpha serum concentration was 1.75 pg/ml (IQR 1.39-2.19 pg/ml) in the pre-procedural sample and 1.69 pg/ml (IQR 1.41-2.29 pg/ml) in the post-procedural. No significant difference in the TNF-alpha concentrations between the samples in the whole studied group was observed (p = 0.91).

TNF-alpha levels and recurrence of arrhythmia

There was no significant difference between TNF-alpha serum concentrations in any of the samples when comparing the recurrence and the non-recurrence groups (for pre-procedural samples: 1.75 pg/ml vs. 1.74 pg/ml; p = 0.72; for post-procedural samples: 1.49 pg/ml vs. 1.79 pg/ml; p = 0.16). No correlation was observed between TNF-alpha serum concentration and the recurrence of AF after both types of ablation procedure (Figures 1 and 2). However, the analysis revealed a significant decrease in the periprocedural

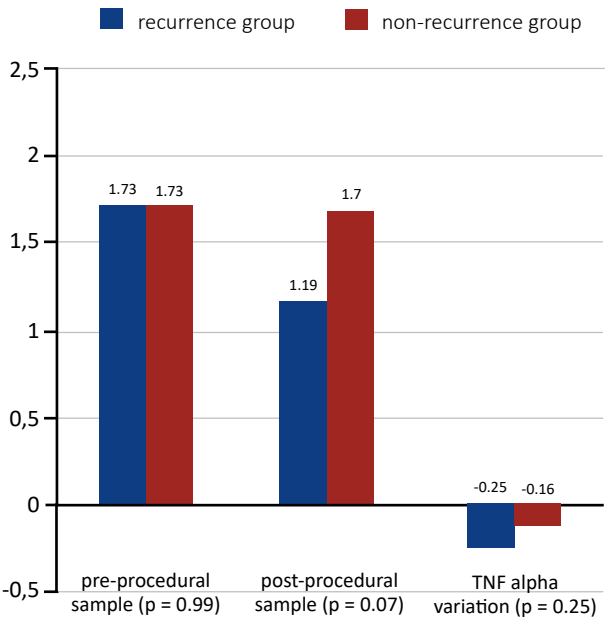

Figure 1. TNF alpha concentrations (pg/ml) and recurrence of arrhythmia in RF ablation group

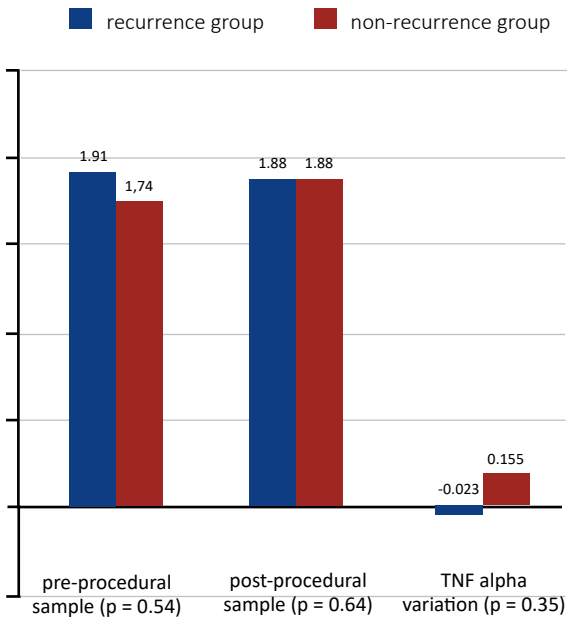

Figure 2. TNF alpha concentrations (pg/ml) and recurrence of arrhythmia in cryoablation group

TNF-alpha serum levels in the recurrence group when the entire study group was analyzed (TNF-alpha variation -0.12 pg/ml vs. 0.05 pg/ml; p = 0.05).

Subanalysis of TNF-alpha concentrations in RF ablation and cryoablation groups

There was no significant difference in the TNF-alpha serum concentrations of the patients from the RF ablation group and cryoablation group in any of the samples (for pre-procedural samples: 1.75 pg/ml vs. 1.78 pg/ml p = 0.86; for post-procedural samples 1.61 pg/ml vs. 1.88 pg/ml p = 0.22).

TNF-alpha levels and other variables

A positive correlation between TNF-alpha levels in the pre-procedural and post-procedural sample was observed ($r = 0.59$; $p < 0.001$). Baseline TNF-alpha serum concentration were not influenced by any of the following variables: age, sex, BMI, median time from diagnosis of arrhythmia, median duration of arrhythmia episode and median atrial fibrillation episodes frequency, renal function, left atrial diameter, time of procedure and summarized time of applications.

Discussion

Although neither pre-procedural nor post-procedural TNF-alpha concentration were associated with ablation outcome, the periprocedural decrease of this parameter was more common in the AF recurrence group. To the best of our knowledge this is the first study that evaluated periprocedural dynamics of TNF-alpha concentrations as a predictive factor for ablation outcome in this selected group of patients. Inclusion of patients with PAF with sinus rhythm and without heart failure prior to the procedure is one of the advantages of presented results.

Our results are opposite to those in the literature, which demonstrate the involvement of TNF-alpha in the pathogenesis of AF and suggest that AF recurrence would be associated with an increased concentration of TNF-alpha or its rise in the periprocedural period [4-7]. However, all our patients had a history of AF. TNF-alpha is one of the basic cytokines which are present in the early stage of the inflammation. This 185-aminoacid glycoprotein peptide hormone is produced mainly by macrophages and monocytes. TNF-alpha stimulates secretion of other proinflammatory factors such as IL-6 and IL-8 initiating the inflammatory reaction [8]. In an animal model of AF it was shown that TNF-alpha induces sustained atrial fibrosis [6] which plays a central role in the pathophysiology of AF [9]. In post-operative AF, TNF-alpha was identified as one of the mediators involved in the alternative pathway of local inflammation caused by surgical incision [10].

Wu et al. showed that an increase in circulating inflammatory factors such as CRP and IL-6 is associated with a higher risk of AF in the general population and patients undergoing CABG and with recurrence of AF after EC or ablation [18].

Frustaci et al. demonstrated that endomyocardial biopsy of the septal region of the right atrium in patients with lone AF showed histological abnormalities (e.g. lymphomononuclear infiltrates, necrosis of the adjacent myocytes, severe hypertrophy, vacuolar degeneration of the atrial myocytes, patchy fibrosis) in contrast to the normal histology results in the control group. Over 60% of patients fulfilled the histological diagnosis of atrial myocarditis, 16.5% of non-inflammatory cardiomyopathy and remaining 16.5% of patchy fibrosis [11]. These discoveries support hypothesis that inflammatory processes that occur in the atria may be a reaction to atrial tissue injury. AF could be therefore one of the manifestations of atrial myocarditis secondary to injury.

On the other hand, it is possible that a decrease in TNF-alpha concentration within the first 24 hours after ablation is an indicator of impaired immunological reaction to myocardial injury resulting in prolongation of the inflammatory process. Moreover, 24 hours might be too short to observe changes in the TNF-alpha concentration in the post-ablation period. Sata et al. showed that TNF-alpha, interleukin 6 and C-reactive protein levels were higher in patients who underwent pharmacological cardioversion because of first AF episode compared with healthy controls. However, no difference was found between TNF-alpha sample taken before cardioversion, 24 hours later and 2 weeks later after conversion to sinus rhythm based on a group of 15 male patients, aged between 41 and 69 years (mean, 58 years) and had no history of organic heart diseases (e.g. valvular or coronary artery diseases and cardiomyopathy). In the control group there were 11 male patients with normal SR (mean age, 57 years; age range, 47 to 67 years) [12].

This may suggest that inflammatory processes related to AF are more profound and systemic. Some epidemiological data show that inflammation is one of the underlying process in AF. In a long-term observation of 2863 participants of the Framingham Offspring cohort, an increase in the inflammatory biomarkers was associated with more frequent incidents of AF [13]. Similar conclusions were drawn by the researchers from the Cardiovascular Health Study [14] and from the paper by Sata et al. [12]. In patients with AF, the TNF-alpha concentration, similarly to other inflammatory biomarkers, was elevated in comparison to the control group. The biomarker profile was different depending on the specific type of AF. TNF-alpha was lower in patients with paroxysmal AF and higher in patients with permanent AF [15].

Rafaqat et al. described the role of metabolic syndrome biomarkers in the pathogenesis of AF. TNF-alpha has been shown to contribute to the pathogenesis of chronic AF. Patients with valvular AF also showed high levels of TNF-α, more severe leukocyte infiltration and greater fibrosis. The level of IL-6 associated with increased left atrial size is a well-known

risk factor for AF. Interleukin-10 and TNF-α levels influenced AF recurrence after ablation [17].

One of the reasons for the lack of differences between pre- and post-procedural concentrations of TNF-alpha might be connected to the fact that ablation using different sources of energy cause specific damage to cardiomyocytes. Although statistically insignificant, we observed that TNF-alpha levels fall after RF ablation, contrary to the concentration in the cryoablation group. In an animal model, Aupperle et al. demonstrated that endocardial cryoablation induces different type of endocardial, transmural and epicardial injury in comparison to RF ablation [16].

Kimura et al. showed that high levels of MMP-2 (Matrix metalloproteinase-2) accompanied by high levels of TNF-α were an independent predictor of AF recurrence [19]. MMP-2 and TNF-alpha levels may be useful in predicting the initial response to the ablation of AF.

Neuromodulation is a new treatment for AF. A study by Stavrakis et al. is the first to investigate the anti-arrhythmic and anti-inflammatory effects of LLTS (low-level tragus stimulation) in humans. 40 patients with paroxysmal AF qualified for ablation were randomly assigned to the 1 h LLTS. Patients were divided into 2 groups of 20 in the LLTS group and the sham control group. There were no statistically significant differences between the groups in the baseline clinical and echocardiographic characteristics. The study consisted of placing a flat metal clip on the tragus causing LLTS (20 Hz) in the right ear (50% lower than the voltage that slows the sinus rhythm). Under general anesthesia, atrial fibrillation was induced by pulsatile atrial stimulation at the beginning and 1 hour of LLTS or sham treatment. Subsequently, blood samples were taken from the patients from the coronary sinus and the femoral vein at the above-mentioned time points. Blood was analyzed for inflammatory cytokines such as TNF alpha and CRP. The study demonstrated for the first time in humans that the duration and inducibility of atrial fibrillation and the levels of inflammatory cytokines were non-invasively suppressed by the low-level transcutaneous electrical stimulation of the tragus [20].

Çetin et al. showed that rosuvastatin reduces the levels of inflammatory cytokines, including TNF-alpha [21]. It can be concluded that rosuvastatin has a protective effect against inflammation. In our study, 13 patients were treated with statins and received their doses of those drugs before and after ablation. The dosing of the drugs was not changed during the periprocedural period. It can be concluded that in our cohort the statins did not have an effect on the dynamic of TNF-alpha levels. This is confirmed by the fact that in 7 patients treated with statins we achieved reductions in TNF-alpha.

Limitations

We did not analyze whether the level of myocardial injury assessed by concentration of myocardial necrosis protein during ablation correlate with TNF-alpha. We did not control other indicators of inflammatory reaction such as C-reactive protein. No correlation between left atrium parameters (LAVi) and AF recurrence was analyzed. We didn't perform comparison analysis or subanalysis in subgroups with hypertension or dyslipidemia. The group of patients included in the study was not large although sufficient to perform reliable statistical analysis. After ablation, antiarrhythmic drugs were discontinued. In the event of AF recurrence, the antiarrhythmic drugs were ordered by the family physician. In our opinion ordering antiarrhythmic drugs did not affect the number of recurrences. Our group was too small for multivariate analysis. This is a preliminary study to a larger study which will take these factors into account.

Clinical implications and future research

Our results show that the periprocedural dynamics of TNF-alpha are involved in the recurrence of AF. Future studies should concentrate on whether influencing the post-ablation healing processes in the atria might result in better scar formation and as a result more effective ablation results. Another question is if the fibrotic processes might be altered in patients with a decrease in TNF-alpha. Obtained data also suggest that injury to atrial tissue caused by RF ablation and cryoablation results in different secretion profile of TNF-alpha. This observation deserves further research.

Conclusion

Neither the pre-procedural nor post-procedural TNF-alpha concentrations are predictive of ablation outcome in patients with PAF. However its periprocedural decrease is associated with AF recurrence. TNF-alpha is a stable biomarker during the periprocedural period in patients with PAF patients undergoing their first ablation procedure.

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Conflicts of interests

None.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the Europea. Eur Heart J [Internet]. 2021 Feb 1;42(5):373-498. Available from: https://doi.org/10.1093/eurheartj/ehaa612
2. Kourliouros A, Savelieva I, Kiotsekoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. Am Heart J [Internet]. 2009;157(2):243-52. Available from: https://www.sciencedirect.com/science/article/pii/S0002870308008909
3. Guo Y, Lip GYH, Apostolakis S. Inflammation in Atrial Fibrillation. J Am Coll Cardiol [Internet]. 2012;60(22):2263-70. Available from: https://www.sciencedirect.com/science/article/pii/S0735109712044907
4. Yamashita T, Sekiguchi A, Iwasaki Y, Date T, Sagara K, Tanabe H, et al. Recruitment of Immune Cells Across Atrial Endocardium in Human Atrial Fibrillation. Circ J [Internet]. 2010;74(2):262-70. Available from: http://www.jstage.jst.go.jp/article/circj/74/2/74_CJ-09-0644/_article
5. Saba S, Janczewski AM, Baker LC, Shusterman V, Gursoy EC, Feldman AM, et al. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-α. Am J Physiol Circ Physiol [Internet]. 2005 Oct 1;289(4):H1456-67. Available from: https://doi.org/10.1152/ajpheart.00733.2004
6. Liew R, Khairunnisa K, Gu Y, Tee N, Yin NO, Naylynn TM, et al. Role of Tumor Necrosis Factor-α in the Pathogenesis of Atrial Fibrosis and Development of an Arrhythmogenic Substrate. Circ J [Internet]. 2013;77(5):1171-9. Available from: https://www.jstage.jst.go.jp/article/circj/77/5/77_CJ-12-1155/_article
7. Lee S-H, Chen Y-C, Chen Y-J, Chang S-L, Tai C-T, Wongcharoen W, et al. Tumor necrosis factor-α alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes. Life Sci [Internet]. 2007;80(19):1806-15. Available from: https://www.sciencedirect.com/science/article/pii/S0024320507001956
8. Wan S, Yim APC. Cytokines in myocardial injury: impact on cardiac surgical approach. Eur J Cardio-Thoracic Surg [Internet]. 1999 Sep 1;16(Supplement_1):S107-11. Available from: https://doi.org/10.1016/S1010-7940(99)00200-6
9. Burstein B, Nattel S. Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation. J Am Coll Cardiol [Internet]. 2008;51(8):802-9. Available from: https://www.sciencedirect.com/science/article/pii/S0735109707037862
10. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. EP Eur [Internet]. 2012 Feb 1;14(2):159-74. Available from: https://doi.org/10.1093/europace/eur208
11. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological Substrate of Atrial Biopsies in Patients With Lone Atrial Fibrillation. Circulation [Internet]. 1997 Aug 19;96(4):1180-4. Available from: https://doi.org/10.1161/01.CIR.96.4.1180
12. Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, et al. C-reactive Protein and Atrial Fibrillation Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J [Internet]. 2004;45(3):441-5. Available from: http://www.jstage.jst.go.jp/article/jhj/45/3/45_3_441/_article
13. Schnabel RB, Larson MG, Yamamoto JF, Kathiresan S, Rong J, Levy D, et al. Relation of Multiple Inflammatory Biomarkers to Incident Atrial Fibrillation. Am J Cardiol [Internet]. 2009 Jul;104(1):92-6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002914909006808
14. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a Risk Factor for Atrial Fibrillation. Circulation [Internet]. 2003 Dec 16;108(24):3006-10. Available from: https://doi.org/10.1161/01.CIR.0000103131.70301.4F
15. Li J, Solus J, Chen Q, Rho YH, Milne G, Stein CM, et al. Role of inflammation and oxidative stress in atrial fibrillation. Hear Rhythm [Internet]. 2010 Apr;7(4):438-44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1547527109013800
16. Aupperle H, Doll N, Walther T, Ullmann C, Schoon H-A, Wilhelm Mohr F. Histological findings induced by different energy sources in experimental atrial ablation in sheep. Interact Cardiovasc Thorac Surg [Internet]. 2005 Oct 1;4(5):450-5. Available from: https://doi.org/10.1510/icvts.2005.109413
17. Rafaqat S. Biomarkers of Metabolic Syndrome: Role in Pathogenesis and Pathophysiology of Atrial Fibrillation. J Atr Fibrillation [Internet]. 2021 Aug 31;14(2). Available from: http://jafib.com/published.php?type=full&id=20200495
18. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: A meta-analysis. Int J Cardiol [Internet]. 2013 Oct;169(1):62-72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167527313016616

19. Kimura T, Takatsuki S, Inagawa K, Katsumata Y, Nishiyama T, Nishiyama N, et al. Serum Inflammation Markers Predicting Successful Initial Catheter Ablation for Atrial Fibrillation. Hear Lung Circ [Internet]. 2014 Jul;23(7):636-43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1443950614000730
20. Stavrakis S, Humphrey MB, Scherlag BJ, Hu Y, Jackman WM, Nakagawa H, et al. Low-Level Transcutaneous Electrical Vagus Nerve Stimulation Suppresses Atrial Fibrillation. J Am Coll Cardiol [Internet]. 2015;65(9):867-75. Available from: https://www.sciencedirect.com/science/article/pii/S0735109714075810
21. Çetin A, Çetin İ, Yılmaz S, Şen A, Savaş G, Çimen B, et al. Oxydative stress markers and cytokine levels in rosuvastatin-medicated hypercholesterolemia patients. 2019;44(4):530-8. Available from: https://doi.org/10.1515/tjb-2018-0267

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RESEARCH ARTICLE

Comorbidities and clinical outcomes of a lung cancer screening trial participants with chronic obstructive pulmonary disease in three-year follow-up

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Abstract

Background: To improve the effectiveness of lung cancer screening using low-dose computed tomography (LDCT), the presence of smoking-related comorbidities that may significantly affect mortality in this group should be taken into account. **Material and methods:** A questionnaire survey and spirometry tests were conducted in a group of 730 respondents as part of a lung cancer screening study between 2016 and 2018. People diagnosed with COPD underwent a three-year follow-up to assess the incidence of medical events. **Results:** Our study confirmed that cardiovascular diseases (CVDs) were the most common comorbidities in patients who were diagnosed with COPD and participated in LDCT lung cancer screening. Among the CVDs, the most common were arterial hypertension (45.8%) and coronary artery disease (12.5%). Tobacco-related diseases (e.g. CVD, lung cancer, and exacerbations of COPD) were the leading causes of emergency department visits and hospitalizations. The number of visits due to COPD in specialized clinics more than doubled in the observed period. **Conclusions:** Properly planned screening tests allow not only for the detection of the disease for which they were designed but also for the assessment of comorbidities. In patients undergoing lung cancer screening, it is justified to extend the diagnostics to include spirometry.

Keywords: chronic obstructive pulmonary disease · diagnostic radiology · oncology · lung cancer · respiratory tract · screening

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide [1]. According to the World Health Organization (WHO), it is the third leading cause of death after coronary artery disease and stroke [2]. The most significant risk factor for COPD is exposure to tobacco smoke [3]. Changes caused by harmful gases and particles lead not only to local inflammatory processes in the airways, but also to systemic inflammation responsible for the considerable comorbidities found in COPD patients [3-5]. According to available data, individuals with COPD have a five-fold higher risk of developing cardiovascular diseases and a two-fold risk of lung cancer compared with smokers without COPD [6-8].

Data from randomized trials targeting the smoking population shows that low-dose computed tomographic (LDCT) screening, through secondary prevention, reduces lung cancer mortality in this group [9-11]. To improve the effectiveness of LDCT screening, trials assessing the potential benefits of combined oncological-pulmonary screening have been conducted in many countries [12-14]. In Poland, there is still not enough epidemiological data about the prevalence of COPD [4]. There is a significant need to assess the impact of lung cancer comobribidities on LDCT screening effectiveness. Therefore, after lung canceer screning programmes, observational studies on medical outcomes of participants are conducted. In this article, we present the data from a three-year follow-up of Polish LDCT screening trial participants in whom complete spirometry was performed to detect COPD.

Patients and methods

To establish the prevalence of main tobacco-related comorbidities among participants of the lung cancer screening program "MOLTEST-BIS: Validation of molecular signatures of early lung cancer in the high-risk group", started in 2016 [15], we conducted an additional investigation to assess the prevalence of COPD. The eligibility criteria were based on the lung cancer screening trial criteria were as follows: aged 50 to 79 years, citizens of Pomeranian Voivodeship, with a smoking history of over 30 pack-years, and either current or former smokers (but only those who had quit smoking no more than 15 years before the screening). Patients provided written informed consent to participate in the study. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (approval No NKBBN/173/2016).

Standardized questionnaire surveys that included questions about the patients' medical histories, previous diseases, medications, smoking histories and respiratory symptoms were distributed. All participants then underwent physical examination and spirometry with a bronchodilator reversibility test.

We established the prevalence and staging of COPD according to the Global Intiative for Chronic Obstructive Lung Disease (GOLD) criteria (3). We also assessed the impact of the disease on quality of life and published that analysis separately [16]. All participants diagnosed with COPD were informed about their spirometry results and the necessity of specialized pulmonary care to implement appropriate treatment. They underwent a three-year follow-up observational study.

In cooperation with the Agency for Health Technology Assessment and Tariff System (AOTMiT) and according to the agreement with the Medical University of Gdańsk, we performed an assessment of participants' main causes of death, hospitalizations and number of COPD-related visits in specialized healthcare centers until the end of 2020. The analyses were performed based on the International Classification of Diseases, Tenth Revision (ICD-10) coded data from Statistics Poland (Główny Urząd Statystyczny).

Patients were identified in the National Health Fund database, which is implemented in the AOTMiT's data archive system. Episodes of hospitalizations, outpatient specialist care and basic medical care (with the main ICD-10 codes) from the period of two years before and three years after the date of examination in the screening trial were arranged chronologically. Then, episodes of visits and hospitalizations by main disease were summarized at six-month intervals, starting from the date of examination. As a result, the number of visits and hospitalizations was presented in the six-month interval periods before and after the date of the study. A different scenario was applied to summarize the number of patients, which was counted incrementally starting from the date of examination in the screening trial. A period of six months was applied, thus the number of patients was presented in six-month follow-up intervals as well as in six-month period intervals before the date of the study. Descriptive statistics were used to summarize and present the data.

Results

The records of 730 participants (335 women and 395 men) from the lung cancer screening program MOLTEST-BIS were analyzed. The mean age of the men and women participating in the study was similar (63.5 vs 63). Based on spirometry results before and after bronchodilator administration, 144 COPD cases (19.7%) were diagnosed (86 men and 58 women). Most cases detected were in the mild stage of the disease, according to the GOLD classification. These results are presented more precisely in a separate article [16].

Table 1 presents the data on the main comorbidities among COPD patients at the beginging of the programme. Comorbidities were recorded based on the questionnaire data. The most common chronic disease reported by the participants was hypertension (45.8%), followed by coronary artery disease (12.5%), diabetes (11.8%) and atrial fibrillation (10.5%). Asthma was reported by 9.7% of the respondents, which required a differential diagnosis with COPD.

The mean duration of follow-up after the screening was 44 months (SD 8.3). We assessed the main causes of death, hospitalizations and visits to specialized healthcare centers among all respondents with COPD diagnoses. Five deaths were reported during the follow-up period. Causes of death according to the ICD-10 code and the most common causes of visits to the Emergency Departments (ED) during three-year observation are presented in Tables 2 and 3, respectively. Most commonly, patients were admitted to the ED due to cardiovascular diseases (CVD), particularly atrial fibrillation (I48) and hypertension (I10). The next most common causes of patients' visits to the ED were lung cancer (C34) and COPD (J44). Additionally, one hospitalization was coded as dyspnoea

Table 1. Illnesses coexisting with COPD

	COPD (N = 144)
Hypertension	66 (45.8%)
Coronary artery disease	18 (12.5%)
Diabetes	17 (11.8%)
Atrial fibrillation	15 (10.5%)
Bronchial asthma	14 (9.7%)
Neoplasm (excluding lung cancer)	11 (7.6%)
Atherosclerosis of lower extremities	11 (7.7%)
Valvular heart disease	10 (6.9%)
Myocardial infarction	7 (4.9%)
Stroke	5 (3.5%)
Atherosclerosis of carotid arteries	4 (2.8%)
Renal failure	3 (2.1%)
Aortic aneurysm	2 (1.4%)

Table 2. Causes of death according to ICD-10

	ICD
Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	I63.5
Atherosclerotic cardiovascular disease	I25.0
Bacterial pneumonia, not specified	J15.9
Malignant neoplasm of overlapping sites of oesophagus	C15.8
Malignant neoplasm of overlapping sites of bronchus and lung	C34.8

Table 3. Causes of visits to the Emergency Department (ED)

	Visits to ED (N = 110)	ICD--10
Cardiovascular diseases	34/110 (31%)	
• Atrial fibrillation	11 (10%)	I48
• Hypertension	10 (9.0%)	I10
• Chest pain	6 (5.4%)	R07
• Atherosclerotic cardiovascular disease	2 (1.8%)	I25
• Palpitations	2 (1.8%)	R00.2
• Observation for suspected myocardial infraction	2 (1.8%)	Z03.4
• Stroke	1 (0.9%)	I63
Lung cancer	16/110 (14.5%)	C34
COPD	12/110 (11%)	J44
Others	46/110 (42%)	

(R06) and another as a different respiratory disorder (J98). Other causes of visits to the ED were reported very rarely.

Table 4 presents the most common causes of hospital admissions. The most common cause of hospitalization was cataracts (17.6%, ICD codes H25 and H26). Additionally, 12.2% of hospitalizations were due to CVD, 7.5% were due to lung cancer and almost 5% were related to COPD. Other causes of hospitalization occurred sporadically and thus have not been analyzed.

Table 5 shows the number of visits to specialized healthcare centers related to COPD before and after the screening program in semi-annual periods. The total number of visits within three years of follow-up was 3384. A two-fold increase in the number of visits related to COPD was found after the screening. There were 95 visits during the two-year pre-screening observation, compared with 212 visits in two years of follow-up and 300 in three years of follow-up.

Table 4. Causes of hospital admissions

Hospital admissions (N = 204)	ICD--10
Cataract	36/204 (17.6%)	H25--26
Cardiovascular diseases	25/204 (12.2%)	
• Atherosclerotic cardiovascular disease	12	I25
• Atrial fibrillation	4	I48
• Stroke	3	I63
• Myocardial infraction	2	I21
• Hypertension	2	I10
• Cardiac arrest	1	I46
• Pulmonary embolism	1	I26
Lung cancer	15/204 (7.3%)	C34
COPD	10/204 (4.9%)	J44
Hernia	7/204 (3.4%)	K40-44
Prostate cancer	5/204 (2.4%)	C61
Breast cancer	4/204 (1.9%)	C50
Pneumonia	3/204 (1.5%)	J15-18
Bronchitis	3/204 (1.5%)	J20
Larynx cancer	3/204 (1.5%)	C32
Others	96/204 (47%)	

Discussion

In many research centers, additional attempts have been made to assess the prevalence of COPD during lung cancer screening programs. These data are heterogeneous and depend on the diagnostic criteria and individual characteristics of the studied population [16]. The prevalence of COPD among participants of lung cancer screening is reported to be as high as 60% [17-18]. In the Polish lung cancer screening program, MOLTEST-BIS, the prevalence of COPD was almost 20% [27]. According to National Lung Screening Trial (NLST) data, mortality from lung cancer, cardiovascular diseases and respiratory failure among patients with COPD in USA increases with the increasing severity of the disease [19]. COPD is a known risk factor for CVD and lung cancer, independent of smoking status [7]. Moreover, patients with COPD tend to have a longer duration of hospitalization and an increased risk of 30-day mortality after myocardial infarction, exacerbations of heart failure and cardiac or surgical procedures [7, 20-21]. To achieve the highest effectiveness of lung cancer screening, it is recommended to pay special attention to participants with coexisting COPD [12, 19, 22-23]. According to epidemiological

Table 5. Number of visits to specialized healthcare centres

All visits	Visits related to COPD
Before the screening trial		
4th semi-annual period	437	15
3rd semi-annual period	429	31
2nd semi-annual period	439	23
1st semi-annual period	402	26
After the screening trial		
1st semi-annual period	554	63
2nd semi-annual period	601	61
3rd semi-annual period	537	50
4th semi-annual period	552	38
5th semi-annual period	568	39
6th semi-annual period	572	49

studies conducted in Europe, CVD is the most common comorbidity associated with COPD, it concerns about 20% patients with COPD and about 9% without COPD [7, 25-26]. According to the GOLD guidelines, in mild and moderate COPD the main causes of death are lung cancer and CVD. Depending on the methodology, they constitute from 12% to 37% causes of death [27].

Our analysis confirmed that the most common comorbidities among participants with COPD were CVDs and the most common among them was hypertension [7, 24-25]. A comorbidity that required particular attention in the differential diagnosis of COPD was asthma, which was reported by 14 participants (9.7%). Due to significant tobacco exposure among these participants, the history of respiratory symptoms and data on asthma diagnosis had to be more specific to exclude the asthma-COPD overlap [3].

Patients were most often admitted to the ED due to smoking-related diseases, such as CVD, lung cancer, and COPD exacerbations, which together accounted for majority of the hospitalizations. Whereas the leading single cause of hospital admission were cataracts and we hypothesize that those could have been due to planned surgical procedures. We recorded a lower number of hospitalizations due to COPD exacerbations compared with other epidemiological studies [26]. This may be related to the early detection of COPD and the provision of feedback information to participants about the diagnosis and the necessity of the immediate start of appropriate treatment.

The effectiveness of the addition of spirometry to the lung cancer screening program was confirmed by a two-fold increase in COPD-related visits to specialized healthcare centers during follow-up (Table 5). Data obtained during the MOLTEST-BIS program indicate that modification of screening programs by implementation of new diagnostic procedures and comorbidity assessment is necessary and improves their effectiveness.

Conclusions

Precisely planned screening programs not only allow us to diagnose a disease that they were designed for but also give us the opportunity to assess patients' comorbidities. Lung cancer screening trials are particularly important in this regard. Among the group of patients with a high burden of active and passive smoking, it is important to broaden the screening to assess the presence of COPD and comorbidities. This would allow those patients to be referred to specialized healthcare centers and receive appropriate treatment, which could prevent the progression of the disease and minimize the risk of future respiratory failure. Further studies are needed to assess the effectiveness of diagnosing and preventing COPD in this group and the possible correlation of our results with the assessment of the severity of emphysema and cardiac calcium scoring using LDCT.

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Conflicts of interests

None.

References

1. Maselli DJ, Bhatt SP, Anzueto A, Bowler RP, DeMeo DL, Diaz AA, et al. Clinical Epidemiology of COPD. Chest [Internet]. 2019 Aug;156(2):228-238. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369219311286
2. The top 10 causes of death, 2000-2016 [Internet]. WHO. 2016 [cited 2018 May 1]. p. 1-9. Available from: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. GOLD. Global Strategy for Prevention, Diagnosis and Management of COPD:2022 Report [Internet]. Global Initiative for Chronic Obstructive Lung Disease. 2022. p. 177. Available from: https://goldcopd.org/2022-gold-reports-2/
4. Śliwiński P, Górecka D, Jassem E, Pierzchała W. Polish Respiratory Society Guidelines for Chronic Obstructive Pulmonary Disease [in Polish]. Adv Respir Med [Internet]. 2014 Apr 30;82(3):227-63. Available from: https://www.mdpi.com/2543-6031/82/3/227
5. Putcha N, Puhan MA, Hansel NN, Drummond MB, Boyd CM. Impact of co-morbidities on self-rated health in self-reported COPD: An analysis of NHANES 2001–2008. COPD J Chronic Obstr Pulm Dis [Internet]. 2013 Jun 28;10(3):324-32. Available from: http://www.tandfonline.com/doi/full/10.3109/15412555.2012.744963

6. Ho C-H, Chen Y-C, Wang J-J, Liao K-M. Incidence and relative risk for developing cancer among patients with COPD: a nationwide cohort study in Taiwan. BMJ Open [Internet]. 2017 Mar 9;7(3):e013195. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2016-013195
7. Rabe KF, Wedzicha JA, Wouters EFM, editors. COPD and Comorbidity [Internet]. European Respiratory Society; 2013. 240 p. Available from: http://erspublications.com/lookup/doi/10.1183/1025448x.erm5913
8. Mouronte-Roibás C, Leiro-Fernández V, Fernández-Villar A, Botana-Rial M, Ramos-Hernández C, Ruano-Ravina A. COPD, emphysema and the onset of lung cancer. A systematic review. Cancer Lett [Internet]. 2016 Nov;382(2):240-4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304383516305444
9. O'Dowd EL, Baldwin DR. Lung cancer screening – low dose CT for lung cancer screening: recent trial results and next steps. Br J Radiol [Internet]. 2018 Oct;91(1090):20170460. Available from: https://www.birpublications.org/doi/10.1259/bjr.20170460
10. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med [Internet]. 2020 Feb 6;382(6):503-13. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1911793
11. Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, et al. Screening for lung cancer: A systematic review and meta-analysis. Prev Med (Baltim) [Internet]. 2016 Aug;89:301-14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091743516300706
12. Regan EA, Lowe KE, Make BJ, Lynch DA, Kinney GL, Budoff MJ, et al. Identifying Smoking-Related Disease on Lung Cancer Screening CT Scans: Increasing the Value. Chronic Obstr Pulm Dis J COPD Found [Internet]. 2019;6(3):233-45. Available from: https://journal.copdfoundation.org/jcopdf/id/1236/Identifying-Smoking-Related-Disease-on-Lung-Cancer-Screening-CT-Scans-Increasing-the-Value
13. Rivera MP, Tanner NT, Silvestri GA, Detterbeck FC, Tammemägi MC, Young RP, et al. Incorporating Coexisting Chronic Illness into Decisions about Patient Selection for Lung Cancer Screening. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med [Internet]. 2018 Jul 15;198(2):e3-13. Available from: https://www.atsjournals.org/doi/10.1164/rccm.201805-0986ST
14. Heuvelmans MA, Vonder M, Rook M, Groen HJM, De Bock GH, Xie X, et al. Screening for Early Lung Cancer, Chronic Obstructive Pulmonary Disease, and Cardiovascular Disease (the Big-3) Using Low-dose Chest Computed Tomography. J Thorac Imaging [Internet]. 2019 May;34(3):160-9. Available from: https://journals.lww.com/00005382-201905000-00004
15. Ostrowski M, Bińczyk F, Marjański T, Dziedzic R, Pisiak S, Małgorzewicz S, et al. Performance of various risk prediction models in a large lung cancer screening cohort in Gdańsk, Poland – a comparative study. Transl Lung Cancer Res [Internet]. 2021 Feb;10(2):1083-90. Available from: https://tlcr.amegroups.com/article/view/41797/html
16. Undrunas A, Kasprzyk P, Rajca A, Kuziemski K, Rzyman W, Zdrojewski T. Prevalence, symptom burden and under-diagnosis of chronic obstructive pulmonary disease in Polish lung cancer screening population: a cohort observational study. BMJ Open [Internet]. 2022 Apr 11;12(4):e055007. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2021-055007
17. Iaccarino JM, Steiling KA, Wiener RS. Lung Cancer Screening in a Safety-Net Hospital: Implications of Screening a Real-World Population versus the National Lung Screening Trial. Ann Am Thorac Soc [Internet]. 2018 Dec;15(12):1493-5. Available from: https://www.atsjournals.org/doi/10.1513/AnnalsATS.201806-389RL
18. Quaife SL, Ruparel M, Beeken RJ, McEwen A, Isitt J, Nolan G, et al. The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach' patients. BMC Cancer [Internet]. 2016 Dec 20;16(1):281. Available from: http://bmccancer.biomedcentral.com/articles/10.1186/s12885-016-2316-z
19. Young RP, Duan F, Chiles C, Hopkins RJ, Gamble GD, Greco EM, et al. Airflow Limitation and Histology Shift in the National Lung Screening Trial. The NLST-ACRIN Cohort Substudy. Am J Respir Crit Care Med [Internet]. 2015 Nov 1;192(9):1060-7. Available from: https://www.atsjournals.org/doi/10.1164/rccm.201505-0894OC
20. Young RP, Hopkins RJ. Chronic obstructive pulmonary disease (COPD) and lung cancer screening. Transl Lung Cancer Res [Internet]. 2018 Jun;7(3):347-60. Available from: http://tlcr.amegroups.com/article/view/21631/16760
21. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-Based Risk for Complications After Transthoracic Needle Lung Biopsy of a Pulmonary Nodule: An Analysis of Discharge Records. Ann Intern Med [Internet]. 2011 Aug 2;155(3):137. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-155-3-201108020-00003
22. Lowry KP, Gazelle GS, Gilmore ME, Johanson C, Munshi V, Choi SE, et al. Personalizing annual lung cancer screening for patients with chronic obstructive pulmonary disease: A decision analysis. Cancer [Internet]. 2015/02/03. 2015 May 15;121(10):1556-62. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cncr.29225

23. Seijo LM, Zulueta JJ. Understanding the Links Between Lung Cancer, COPD, and Emphysema: A Key to More Effective Treatment and Screening. Oncology (Williston Park) [Internet]. 2017;31(2):93-102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28205188
24. Du Y, Li Q, Sidorenkov G, Vonder M, Cai J, de Bock GH, et al. Computed Tomography Screening for Early Lung Cancer, COPD and Cardiovascular Disease in Shanghai: Rationale and Design of a Population-based Comparative Study. Acad Radiol [Internet]. 2021 Jan;28(1):36-45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1076633220300489
25. Mapel DW, Hurley JS, Frost FJ, Petersen H V, Picchi MA, Coultas DB. Health Care Utilization in Chronic Obstructive Pulmonary Disease. Arch Intern Med [Internet]. 2000 Sep 25;160(17):2653. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.160.17.2653
26. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res [Internet]. 2010 Dec 10;11(1):122. Available from: http://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-11-122
27. GOLD. Global Initiative for Chronic Obstructive Lung Disease [Internet]. 2021. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.0-11Nov20_WMV.pdf
28. Barr RG, Celli BR, Mannino DM, Petty T, Rennard SI, Sciurba FC, et al. Comorbidities, Patient Knowledge, and Disease Management in a National Sample of Patients with COPD. Am J Med [Internet]. 2009 Apr;122(4):348-55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002934308010723
29. Franssen FME, Rochester CL. Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? Eur Respir Rev [Internet]. 2014 Mar 1;23(131):131-41. Available from: http://err.ersjournals.com/cgi/doi/10.1183/09059180.00007613
30. Terzano C, Conti V, Di Stefano F, Petroianni A, Ceccarelli D, Graziani E, et al. Comorbidity, Hospitalization, and Mortality in COPD: Results from a Longitudinal Study. Lung [Internet]. 2010 Aug 12;188(4):321-9. Available from: http://link.springer.com/10.1007/s00408-009-9222-y

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RESEARCH ARTICLE

Comparison of the O-arm and C-arm guided pedicle screw placement

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Abstract

Background: Transpedicular screw placement remains the gold standard technique for stabilization of the lumbar spine. **Material and methods:** This is a retrospective study that analyzes patients that underwent the spinal stabilization surgical procedure. We compared results from two independent neurosurgical centers. In the years 2012-2015, the O-arm and StealthStation neuronavigation system was used for implantation of transpedicular screws. From 2018 to 2020 the transcutaneous pedicle screw placement procedure was performed using a standard C-arm device. **Results:** In 208 procedures performed with the O-arm device, the accuracy of screw position was 98.08%. Screw repositioning was necessary in 1.92% of all cases. In the 30 procedures that were performed using the C-arm, the accuracy of the screws was 86.7% and the screw reposition procedure accounted for 10% (in one case screws were not replaced due to clinical sequelae). **Conclusions:** Our data show that the spinal fusion with the O-arm tool has more accuracy, thus might be more indicated in procedures that require minimally invasive spinal stabilization.

Keywords: spine surgery · transpedicular screws · minimally invasice surgery · O-arm · C-arm

Citation

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TRANSPARENT PROCESS OPEN ACCESS

Introduction

There are many causes of spinal instability e.g. to trauma, congenital abnormalities, tumor invasion and degenerative process. Changes in lifestyle of the majority of the population and increasing incidence of obesity, directly contributes to high demand for low back pain treatment because of the destabilization as the part of the degenerative process. Because of the reduction in muscle mass along with increasing body weight, the degenerative processes of the vertebral discs and facet joints lead to spinal destabilization. This process can present with spondylolisthesis of the adjacent spinal motor segments.

At the same time, patient's are increasingly interested in minimally invasive treatment with the maximum reduction of the stress associated with surgery (e.g. reduced time of hospitalization and reduced need for painkillers). Spinal stabilization system with neuronavigation seems to meet those demands. In this article we present the results of such procedures in comparison with C-arm technique. In the beginning of the learning curve, we encountered technical problems which contributed to the prolongation of the procedure. Nevertheless, gained experience allowed us to significantly shorten the procedure time and to preserve its safety and accuracy.

Correct placement of the screws was widely discussed in the literature (Fig. 1) [1-3]. However, still it is difficult to assess the spinal destabilization by referring to one imaging method. Secondly, sufficient level of spine stabilization differs amongst patients and directly depends on their age, lifestyle and expected quality of life. Degenerative spondylolisthesis may show that the destabilization process did occur, although due to natural progression of the degenerative process the spine became re-stabilized, therefore there is no need for screw implantation. In some neurosurgery centers, placement of intervertebral implant is a standalone indication for bilateral transpedicular stabilization. Since the removed vertebral disc accounts in 80% for motor segment stabilization and intervertebral arthrodesis is a prolonged process. The literature does not describe clear advantages of any technique over another [4-5]. In recent years, placement of the screws could be easily planned using the O-arm navigation technique, which was first introduced in 2006. Thus, it is possible to plan the exact position of the screw not only in the pedicle and also in the vertebral body in order to avoid damage of the adjacent vessels. Although this technique seems to be very accurate with low number of side effects reported, there are still updates of inappropriate screw placement or displacement of implanted material due to insufficient bone fusion.

The exact criteria for screw reposition are still unclear. Taking into consideration only clinical criteria, e.g. post-operative pain of the spine or post-operative pain radiating to the lower limbs, seems to be insufficient to asses screw placement. Literature shows that clinical symptoms along with inappropriate screw placement that violates more than 4 mm in the pedicle, is an indication to reposition the screws [6]. More confounding might be the fact that some patients do not report any symptoms, despite the fact that their computed tomography (CT) scan shows inappropriate screw placement which violates pedicle or pierces the vertebral body. Moreover, appropriate fixation of the screws correlates not only with good transition through the pedicle but also depends on the bone density and its availability to heal.

When comparing the C-arm to O-arm stabilization, the accuracy of pedicle screw placement seems to be the main advantage pointing on the O-arm technique [7-10]. Nevertheless, there is still a concern about high radiation exposure, due to the necessity to perform a 3 dimensional (3D) CT scan before and after the procedure. We should not forget about the fact that one CT scan provides the radiation exposure that is acceptable for one patient in one year period [11]. Based on the recent literature, it seems to be clear that this radiation exposure might be substantially reduced by obtaining a low-dose 3D scan, which offers acceptable imaging quality [12-15].

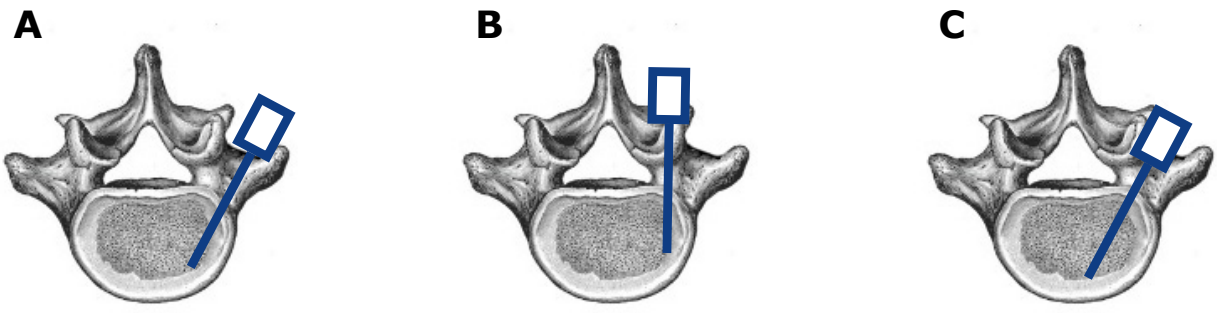

Figure 1. Types of screw corridor in transpedicular spinal fusion. A – transcortical screw placement, B – insertion through pedicle with engagement of the transverbal joint, C – insertion through pedicle without joint involvement

Material and Methods

In a 4-year period (2012-2015) a total of 208 transpedicular stabilization procedures were performed using the O-arm Surgical Imaging with StealthStation navigation system (Medtronic USA/Ireland). Clinical data were analyzed retrospectively. There were 106 males (51%) and 102 (49%) females in the research group. Their age varied from 20 to 95 years (median 56.5 years). Majority of the patients were in 5th or 6th decade of life. Lumbar stabilization was obtained in 93% and thoracic stabilization in 7% of the cases. Trauma was the indication for the spinal stabilization in 10.6% of the cases. Screw insertion was done by the same operator in 86.5% of all cases. In summary, four surgeons where performing the transpedicular screw placement procedure. Whereas, neuronavigation planning procedure was done by other three surgeons. Standard screws with 5.5 mm diameter were used in all procedures. The length of the screws was assessed based on an intra-operative CT scan performed using the O-arm device.

In a 2-year period (2018-2020) 30 transpedicular stabilization procedures using the C-arm (Siemens, Germany) were performed. There were 12 (40%) females and 18 (60%) males in this research group. The patients' age varied from 28 to 75 years (median 58.5 years). Lumbar stabilization was obtained in 76.7% of the cases, thoracic stabilization in 23.3%. In 30% of the cases trauma was the indication for spinal stabilization. There were more than five different operators performing surgery. In all cases standard 5.5 mm screws were used. Postoperative CT scan was done in 50% of the cases and it was always performed when patient had reported significant postoperative pain symptoms. In 3 cases (10%), reposition procedure was done with satisfactory outcome. One patient was not re-operated despite of inappropriate screw placement. Although the screw has been positioned in the S1 recess and it violated more than 4mm of the pedicle, the patient did not report any symptoms and the stability of the implanted material was not compromised, we decided not to perform surgery.

As we progressed along the learning curve, we made some modifications to the O-arm screw fusion procedure resulting in shorter operation time and lower dose of radiation applied to the patient and personnel in the operating room. In the years 2012-2013, the 3D scan was performed after every stabilization procedure. After year 2013, the 3D scan was performed only in case of suspected incorrect screw placement. Multiplanar images were assessed in the operating room by the operator and surgeon involved in planning procedure. If a 3D scan was not performed postoperatively and patient reported clinical symptoms, a CT scan was obtained (usually on the day of the operation) to precisely assess screw placement. When screw implantation of all the screws was not possible due to difficult anatomical conditions, previously placed screws were removed and only nerve root decompression was performed.

Pedicle breach was suspected post-operatively when the patient reported clinical symptoms such as radicular pain (radiating to the lower limb) or low back pain. However, post-operative pain rarely was due to inappropriate screw placement, because the pain has subsided without intervention during standard post-operative hospitalization period. CT imaging studies were reviewed by the radiologist and the operator that performed the procedure. Incorrect position of the screws was recognized on the CT scan in case of conflict of the screw with nerve structures or when the position of the screws could suggest instability of the implanted material.

Depending on the patien's diagnosis and clinical symptoms, additional nerve root decompression or discectomy was performed. Patient was placed in the prone position on a carbon table to ensure adequate X-ray radiation translucency. Placement of the screws was always performed through the guide rod that confirmed the proper entrance of the screws along the planned trajectory.

Side of the decompression was chosen on the basis of imaging studies and clinical symptoms of radiculopathy, such as positive straight leg raise test (positive Lasègue sign) and pain distribution consistent with a given dermatome. To qualify a patient for the procedure, clinical symptoms had to be consitent with the radiological findings. If the patient needed nerve root decompression, in all cases it was done before the stabilization procedure, in order to preserve the conditions after nerve root decompression. In patients diagnosed with spondylosis, screw fixation was done unilaterally. In all cases of spondylolisthesis bilateral stabilization was obtained to ensure appropriate segmental stabilization.

The O-arm system with Stealth Station provides 2- and 3-D images of the spine. A 3D image is necessary to plan the insertion of the screws, thus it was performed after the navigation frame was placed. The scanned image is merged and gives real-time position of the certain tools that are used intraoperatively, based on the reference frame that registers appropriate 3D image in space. Besides 3D navigation, the O-arm is still used with the C-arm function during the operation. It is based on surgeon preferences to assess appropriate placement of the wires which guide the trajectory for the screw placement. The screws are placed transcutaneously to minimize tissue trauma, in contrast to the open procedure where a large group of the paraspinal muscles has to be dissected. The length of the screws depends on anatomical conditions shown in the 3D scan. Planning was done in the operating theatre prior to the procedure.

Results

Of the 208 cases of transpedicular stabilizations performed using the O-arm device in years 2012-2015, 93% were lumbar and only 7% thoracic. Accuracy rate of the screw positioning was 98.08% and reposition rate was 1.92% (5 pa-

tients, Tab. 1). In the group of patients who required screw reposition, 4 required lumbar and one thoraco-lumbar stabilization. Among patients that needed screw revision, in 4 cases inappropriate screw position was detected in the 3D scan that was performed at the end of the operation (Fig. 2). In case of one patient the 3D scan was not done in the operating theater and the inappropriate screw position was noted in the CT scan that was ordered because of his clinical symptoms. Infection rate was 0.48% (1 patient) and multiple antibiotics were needed due to resistant infection. No screw displacement was found in that patient.

Table 1. Comparison of C-arm vs O-arm techniques

	C-arm	O-arm
Screw accuracy	86.67%	98.08%
Screw reposition rate	10.00%	< 2%
Average hospitalization (days)	3	2
Postoperative CT scan	50% of cases	Only when symptoms < 2%

In 67 cases spondylolisthesis was the indication for surgery (32.2%). Spondylosis, defined as the degeneration of intervertebral discs of different etiologies, was the indication for surgery in 42.3% of cases (88 patients). Trauma was an indication for surgery in 21 cases (10% of all cases), discopathy with low back pain 7.2% (15 patients) and tumor 2.4% (5 patients).

In the 30 procedures performed using the C-arm, the accuracy of the screws was 86.67% and the screw reposition procedure accounted for 10%. In case of one patient, the radiological exam revealed a screw inside the S1 recess. He was not qualified for the reposition procedure because of lack of symptoms. In both the C-arm and O-arm research groups there were no concerns about the stability of the entire transpedicular fixation system. In the C-arm group 23% of cases (7) were due to traumatic fracture. 73% (13) cases were due to spondylotic degenerative changes. Median hospitalization time was shorter in the O-am group (2 days), compared to the C-arm patients (3 days).

Discussion

Minimal invasiveness seems to be the most important goal from the perspective of the patients, doctors and the costs. The comparison of both groups shows advantages of the O-arm procedure in respect of the minimal invasion, accuracy and safety of the procedure. Although the price of the O-arm device might limits its universal use, one should not ignore factors such as reduction of the hospitalization time and cost of analgesia. Further health economics studies are needed to assess these factors [1, 2].

As we gained experience in performing the O-arm procedure, we observed improvement in the process and the possibility to skip some of the steps recommended by the manufacturer, allowing us to reduce the radiation exposure for patients and medical staff, without additional complications or side effects. Even the low-dose 3D O-arm scan is

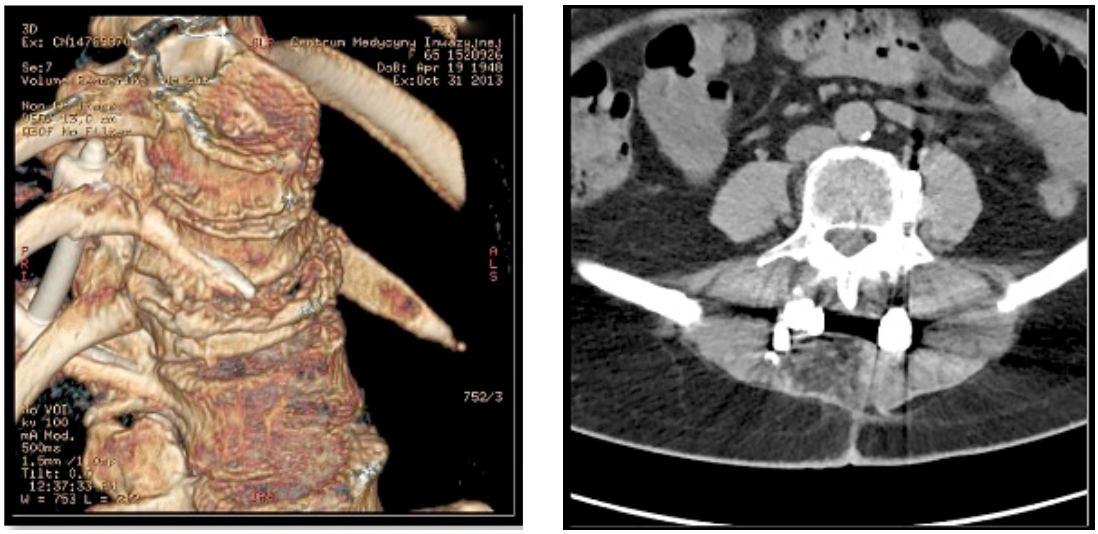

Figure 2. Post-operative CT scan revealed inappropriate screw placement, in this case outside the vertebral body, which caused insufficient support for the spinal stabilization

connected with high radiation exposure [15, 16]. It seems beneficial to not obtain the second (post-operative) 3D scan unless it is indicated. Abandoning the post-operative 3D scan was not associated with a higher need for reposition of implanted screws. In summary, 4 out of 5 inappropriately placed screws were suspected by the operator and the additional 3D scan was done to assess their position. In one case the post-operative 3D scan was not obtained, however that procedure was performed by a surgeon who did not have experience in the O-arm procedure. The accuracy rate of 98.08% is comparable to that reported in the literature (97.5%) [17].

Those results confirm that the O-arm technique is very accurate in planning and placing transpedicular screws. Furthermore, it is associated with very low incidence of infection due to the fact that small incisions were required for this procedure. Due to low traumatization of the tissue, patient group required less amounts of analgesics and typical length of postoperative hospitalization was only two days.

While gaining the experience with the O-arm implantation technique some problems appeared, which marked the importance of certain steps during the operation procedure that required additional precautions. The main issue was to implant the reference frame correctly with most stability on the spinous process and then to supervise its position to avoid picture shift during merging. Among some groups of patients, we have encountered the anatomical disproportion of the pedicles. Available screws were too large to place them safely in the pedicles without anatomical compromise of the periosteum. Amongst some of the patients, particularly in the L5-S1 region, the anatomical relations prevent appropriate titanium bar placement. In these cases, the curvatures of the spine were of great importance. The inappropriate angle between the L5 vertebrae and the iliac crest made it much more difficult or even in some cases impossible to place the titanium stabilization bar. For this reason, in some cases conversion to the open surgical procedure was necessary.

Among patients with large amounts of subcutaneous tissue in the lower back area, we observed difficulties in placing the titanium bar near the lamina, due to the limitation of the device used. Despite the fact that screw placement was planned using neuronavigation station, it was impossible to match the titanium bar with the screw cups. A preferred solution turned out to be implantation of longer screws which gave better access to their cups, where titanium bar was placed.

Analysis of the O-arm reposition group revealed that frame shift was the main cause of inappropriate screw implantation. Adequate reference frame fixation is critical, when trying to avoid shifting complications. Moreover, the analysis indicated that the planned position of the screws on the lateral side of the pedicle reduces the risk of instability of the implanted screws. In the following years, exposure to X-ray radiation was reduced by obtaining only low-dose 3D scans and by verifying the position of the screws in 2D scans, thus reducing the radiation dose both for the patient and staff.

21 patients were qualified to O-arm stabilization procedure because of trauma. Stabilization was performed by fixing the healthy vertebra with each other, one below the fracture and one above. No additional healthy vertebral levels were used to reinforce the stabilization strength. Despite the fact that no additional levels were included in transpedicular fusion, no displacement or signs of destabilization were seen. However, in the group of trauma patients, it was necessary to perform another 3D scan after unilateral stabilization, because of the change of anatomical relations and in order to prevent damage to neuronal structures.

The O-arm guided transpedicular stabilization seems to be a reliable and minimally invasive method. This observation was also confirmed in double-blinded studies at unrelated neurosurgical centers and meta-analyses [1-3].

Conclusions

Despite the initially prolonged surgical time, the O-arm guided transpedicular stabilization becomes more intuitive the more often it is used, thus the learning curve contributes to more efficient and faster procedure without side effects along the line. Consequently, the initial investment in expensive equipment might be justified by avoiding the potential cost-generating adverse effects, prolonged hospitalization and higher doses of pain medications. Nevertheless, those hypotheses have to be investigated in other studies.

Funding

None.

Conflicts of interest

None.

References

1. Feng W, Wang W, Chen S, Wu K, Wang H. O-arm navigation versus C-arm guidance for pedicle screw placement in spine surgery: a systematic review and meta-analysis. Int Orthop [Internet]. 2020 May 7;44(5):919–26. Available from: http://link.springer.com/10.1007/s00264-019-04470-3

2. Shin M-H, Ryu K-S, Park C-K. Accuracy and Safety in Pedicle Screw Placement in the Thoracic and Lumbar Spines: Comparison Study between Conventional C-Arm Fluoroscopy and Navigation Coupled with O-Arm® Guided Methods. J Korean Neurosurg Soc [Internet]. 2012;52(3):204. Available from: http://jkns.or.kr/journal/view.php?doi=10.3340/jkns.2012.52.3.204
3. Tabaraee E, Gibson AG, Karahalios DG, Potts EA, Mobasser J-P, Burch S. Intraoperative Cone Beam–Computed Tomography With Navigation (O-ARM) Versus Conventional Fluoroscopy (C-ARM): A Cadaveric Study Comparing Accuracy, Efficiency, and Safety for Spinal Instrumentation. Spine (Phila Pa 1976) [Internet]. 2013;38(22). Available from: https://journals.lww.com/spinejournal/Fulltext/2013/10150/Intraoperative_Cone_Beam_Computed_Tomography_With.19.aspx
4. Ambati D V, Wright EK, Lehman RA, Kang DG, Wagner SC, Dmitriev AE. Bilateral pedicle screw fixation provides superior biomechanical stability in transforaminal lumbar interbody fusion: a finite element study. Spine J [Internet]. 2015;15(8):1812–22. Available from: https://www.sciencedirect.com/science/article/pii/S1529943014006469
5. Chen C, Cao X, Zou L, Hao G, Zhou Z, Zhang G. Minimally invasive unilateral versus bilateral technique in performing single-segment pedicle screw fixation and lumbar interbody fusion. J Orthop Surg Res [Internet]. 2015;10(1):112. Available from: https://doi.org/10.1186/s13018-015-0253-1
6. Costa F, Villa T, Anasetti F, Tomei M, Ortolina A, Cardia A, et al. Primary stability of pedicle screws depends on the screw positioning and alignment. Spine J [Internet]. 2013;13(12):1934–9. Available from: https://www.sciencedirect.com/science/article/pii/S1529943013003963
7. Bolger C, Kelleher MO, McEvoy L, Brayda-Bruno M, Kaelin A, Lazennec J-Y, et al. Electrical conductivity measurement: a new technique to detect iatrogenic initial pedicle perforation. Eur Spine J [Internet]. 2007;16(11):1919–24. Available from: https://doi.org/10.1007/s00586-007-0409-8
8. Tian N-F, Xu H-Z. Image-guided pedicle screw insertion accuracy: a meta-analysis. Int Orthop [Internet]. 2009;33(4):895––903. Available from: https://doi.org/10.1007/s00264-009-0792-3
9. Kosmopoulos V, Schizas C. Pedicle Screw Placement Accuracy: A Meta-analysis. Spine (Phila Pa 1976) [Internet]. 2007;32(3). Available from: https://journals.lww.com/spinejournal/Fulltext/2007/02010/Pedicle_Screw_Placement_Accuracy__A_Meta_analysis.22.aspx
10. Costa F, Cardia A, Ortolina A, Fabio G, Zerbi A, Fornari M. Spinal Navigation: Standard Preoperative: Versus: Intraoperative Computed Tomography Data Set Acquisition for Computer-Guidance System: Radiological and Clinical Study in 100 Consecutive Patients. Spine (Phila Pa 1976) [Internet]. 2011;36(24). Available from: https://journals.lww.com/spinejournal/Fulltext/2011/11150/Spinal_Navigation__Standard_Preoperative__Versus_.15.aspx
11. Santos ERG, Ledonio CG, Castro CA, Truong WH, Sembrano JN. The Accuracy of Intraoperative O-arm Images for the Assessment of Pedicle Screw Postion. Spine (Phila Pa 1976) [Internet]. 2012;37(2). Available from: https://journals.lww.com/spinejournal/Fulltext/2012/01150/The_Accuracy_of_Intraoperative_O_arm_Images_for.19.aspx
12. Gertzbein SD, Robbins SE. Accuracy of pedicular screw placement in vivo. Spine (Phila Pa 1976) [Internet]. 1990;15(1):11––4. Available from: http://europepmc.org/abstract/MED/2326693
13. Esses SI, Bednar DA. The spinal pedicle screw: techniques and systems. Orthop Rev [Internet]. 1989;18(6):676–82. Available from: http://europepmc.org/abstract/MED/2664668
14. Suresh P, M. LE, L. BE, Hiroyuki Y, V. PV. Pedicle Screw Placement With O-arm and Stealth Navigation. Orthopedics [Internet]. 2012 Jan 16;35(1):e61–5. Available from: https://doi.org/10.3928/01477447-20111122-15
15. Abul-Kasim K, Söderberg M, Selariu E, Gunnarsson M, Kherad M, Ohlin A. Optimization of Radiation Exposure and Image Quality of the Cone-beam O-arm Intraoperative Imaging System in Spinal Surgery. Clin Spine Surg [Internet]. 2012;25(1). Available from: https://journals.lww.com/jspinaldisorders/Fulltext/2012/02000/Optimization_of_Radiation_Exposure_and_Image.8.aspx
16. Su AW, Luo TD, McIntosh AL, Schueler BA, Winkler JA, Stans AA, et al. Switching to a Pediatric Dose O-Arm Protocol in Spine Surgery Significantly Reduced Patient Radiation Exposure. J Pediatr Orthop [Internet]. 2016 Sep;36(6):621–6. Available from: https://journals.lww.com/01241398-201609000-00012
17. Van de Kelft E, Costa F, Van der Planken D, Schils F. A Prospective Multicenter Registry on the Accuracy of Pedicle Screw Placement in the Thoracic, Lumbar, and Sacral Levels With the Use of the O-arm Imaging System and StealthStation Navigation. Spine (Phila Pa 1976) [Internet]. 2012;37(25). Available from: https://journals.lww.com/spinejournal/Fulltext/2012/12010/A_Prospective_Multicenter_Registry_on_the_Accuracy.15.aspx

EUROPEAN JOURNAL OF TRANSLATIONAL
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RESEARCH ARTICLE

Comparative study on awareness about carpal tunnel syndrome among dental professionals in India and Malaysia

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Abstract

Introduction: Carpal Tunnel syndrome (CTS) is a common medical condition that occurs when the median nerve is compressed at the carpal tunnel. Many people, particularly females, in the general population are affected with CTS. This study aims to determine the level of awareness of CTS among dental professionals in India and Malaysia. **Material and Methods:** The cross-sectional study was carried out among dentists in India and Malaysian, from August 2020 to November 2020. 150 professional dentists with a minimum of one year of work experience were included in the study. Dentists who worked full-time as academicians were excluded. The survey form was circulated using WhatsApp. The SPSS software package was used to analyze the data collected from the sample. **Results:** Both Indian and Malaysian participants thought that the main symptom is tingling and numbness. Both groups stated that minimizing the stress on the wrist would prevent CTS. 100% of Malaysian participants thought that CTS could affect job performance, though those from Indian marked that it also affects social life and sleep. **Conclusion:** The awareness of CTS among both Indian and Malaysian dentists was adequate. Furthermore, there is a strong correlation between CTS and chronic disease like rheumatoid arthritis.

Keywords: carpal tunnel · clinical signs · prevention · treatment · awareness

Citation

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TRANSPARENT PROCESS OPEN ACCESS

Introduction

Carpal Tunnel syndrome (CTS) is a common medical condition that occurs when the median nerve is compressed at the carpal tunnel [1]. It may also describe radiculopathy or peripheral neuropathy [2]. In CTS, the pressure is increased within the carpal tunnel; therefore it reduces the movement at the level of wrist [3]. The clinical symptoms include burning sensation and paresthesia in digits except the ulnar half of fourth (ring) and fifth (little) fingers [4]. These symptoms are exacerbated at night and in the morning [5]. In order to relieve discomfort or symptoms, patients flick or 'shake out' their hand at the level of the wrist (flick sign) [6]. If not treated, CTS may lead to wasting and atrophy of thenar muscles.

Nearly 3.5% of the general population is considered to have CTS [7]. Women are more likely to acquire CTS than men due to hormonal changes [8]. CTS is mostly diagnosed with the age group between 30 and 60 years. According to the literature, we can expect that at least one in every five symptomatic individuals has CTS. The first step in diagnosing CTS is paying attention to the presence of distinctive symptoms in the patient's history. The physical examination of the patient's hand is a critical step in the diagnosis of CTS since certain findings may suggest the presence of other causes. The Tinel sign and Phalen manoeuvre are the initial diagnostic procedures for CTS during the physical examination [7, 9-10].

Certain medical conditions increase the risk of developing CTS, e.g. hypothyroidism, arthritis, and high blood pressure [10]. Lifestyle can also increase risk of CTS, e.g. sedentary lifestyle, pregnancy, high salt intake and increase body mass index [11]. Dental professionals are at increased risk of developing CTS due to repetitive hand motions in their clinical practice [12]. CTS is a serious diagnosis for dental professionals, as they rely on full range of motion and sensation in hands in order to perform procedures. Considering the importance of this syndrome and its high incidence among dentists, we aimed to study the level of awareness about CTS among dental professionals in India and Malaysia.

Materials and methods

The cross-sectional study was carried out among dentists in India and Malaysian, from August 2020 to November 2020. 150 professional dentists with a minimum of one year of work experience were included in the study; dentists who worked full-time as academicians were excluded. Ethical Committee approval was obtained from the Saveetha Institute of Medical and Technical Sciences (SIMATS). We prepared a 6-item, multiple-choice questionnaire (see Supplementary Materials) and made it available online until we reached the target sample size. The survey form was circulated through WhatsApp and only those who agreed on the consent form could take up the survey else they cannot proceed further. The IBM SPSS version 23 (Armonk, NY, United States) package was used to analyze the data and calculate the Pearson chi squared test.

Results

A total of 150 dentists were participated in our study. In the present study, the awareness level of both Indian and Malaysians about CTS is ample. Both Indian and Malaysian participants thought that the main symptom is tingling and numbness. Both populations were suggested that minimizing the stress on the wrist would prevent CTS. 100% of Malaysian participants thought that CTS could affect job performance, though the Indian participants marked that it also affects social life and sleep. Least number of people from both populations believed to wear a splint during sleep to keep wrist in straight would be effective on CTS (Figure 3). 26% of Indians and 15% of Malaysians believed that splint is the one of the main treatments for CTS. 16% of Malaysians and 15% of Indians believed that NISAD is the second-best treatment for CTS. 100% of Malaysian's thought that CTS affects job concert, but Indians suspected that 75% affect job, 11% sleep and 14% of them felt affecting the social life (Figure 1). Rheumatoid arthritis (RA) people have the higher chance of developing CTS which was thought by Indians and Malaysians. But very few Malaysians believed hypothyroidism too (Figure 2).

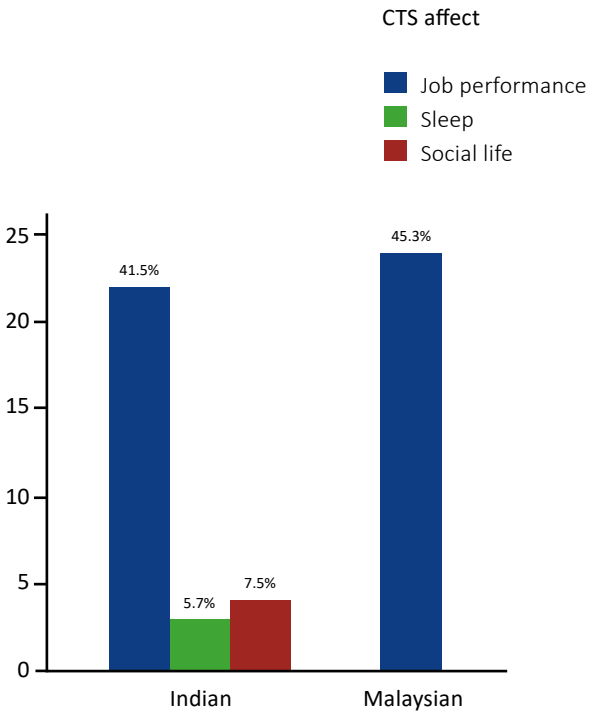

Figure 1. Both Indian and Malaysian participants were aware of CTS effect on job performance (p = 0.03)

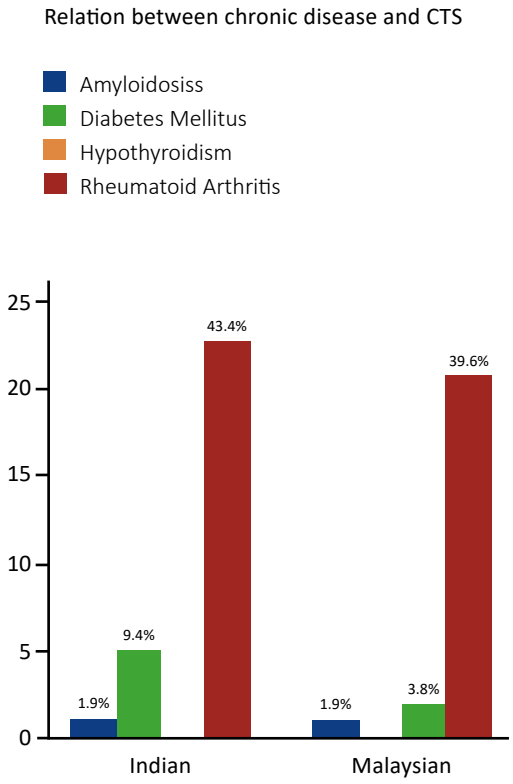

Figure 2. Indian participants were more aware that people suffering from rheumatoid arthritis have a greater risk of CTS (p = 0.08)

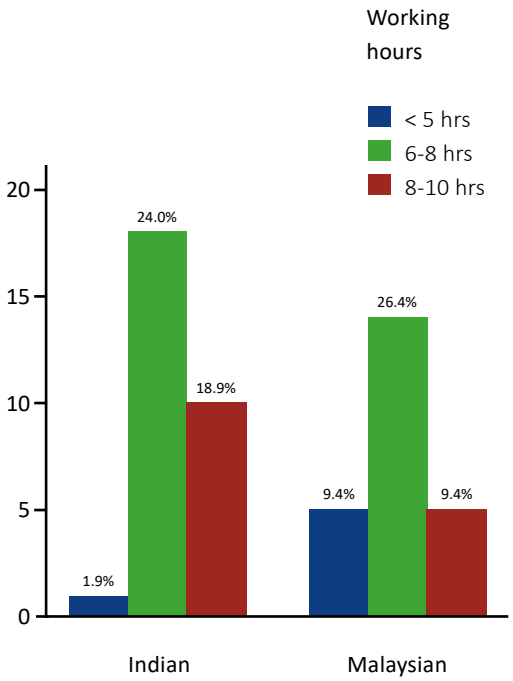

Figure 3. Indian participants stated that they were working for 6-8 hrs more per day than Malaysians (p = 0.11)

Disscussion

Most of the Indian and Malaysian dentists work for 6-7 hours per day and very few only work less than five hours per day (Figure 3). The more time the dentist spends working, the more chances of occurrence of CTS symptoms. A previous study in the Saudi population showed that increased hand pain and symptoms are evident in those who are working with patients for more than eight hours [12]. In addition, earlier studies revealed that dentists who worked for extensive hours were more likely to develop CTS [13-14]. In our study, both the Indian and Malaysian dentists agreed that tingling and numbness in the thumb, index and middle finger is the main clinical feature of CTS. The second most commonly reported clinical feature reported by both groups was pain in the wrist, then overall decrease of hand grip strength (Figure 4). Haghighat et al determined the CTS based on numbness of fingers [15]. In several studies it was reported that dentists suffering from CTS complained of having severe pain in the hand and wrist [16-17]. In the present study, both Malaysians and Indians were not aware that pain in the wrist is the foremost clinical feature of CTS. In a study by Page et al, more than 10% of participants noted that avoiding repetitive movement also prevents CTS, which is disparate to our present study (Figure 5) [18].

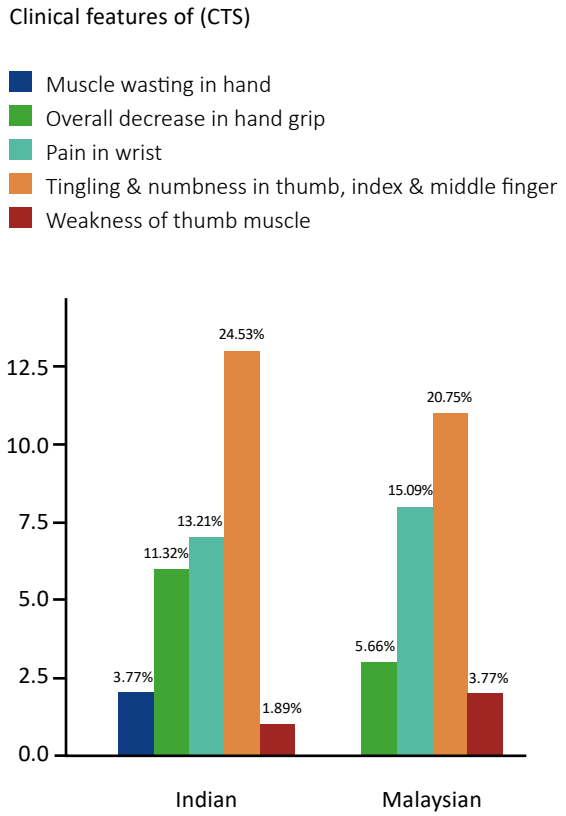

Figure 4. Indian participants were more aware about the clinical features of CTS (p = 0.53)

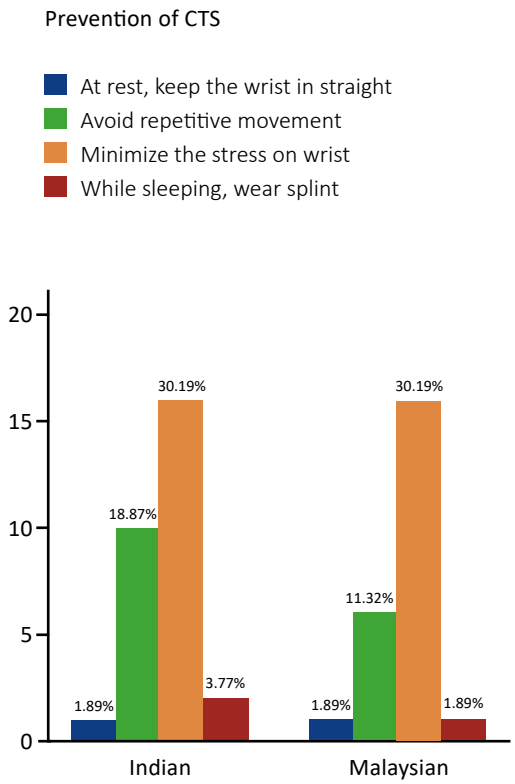

Figure 5. Indian participants were more aware that avoiding repetitive movement can prevent CTS (p = 0.83)

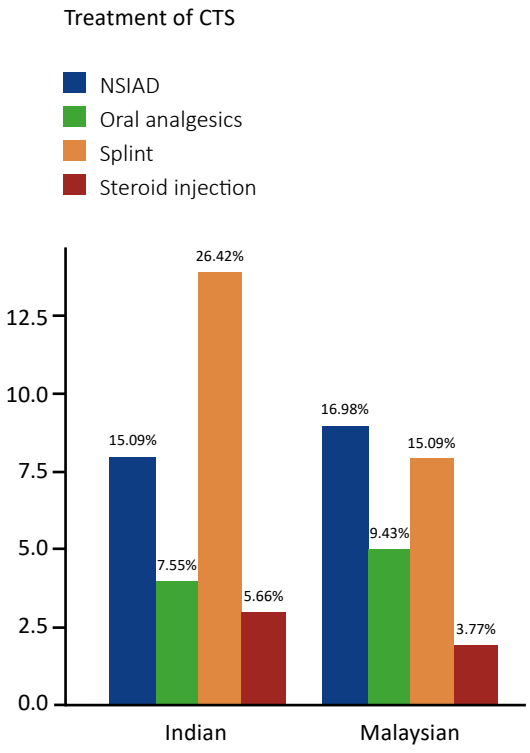

Figure 6. Malaysian participants were more aware of oral analgesics in the treatment of CTS (p = 0.67)

Wellman et al reported that changing tools and tasks, thus decreasing recurrent wrist movements, were steps to prevent CTS [19]. By increasing the number of breaks, reducing work hours, and decreasing the recurrent wrist movement would prevent the CTS [20]. Alyousef et al revealed that oral analgesics and splint are most used to cure CTS [21]. However in our study, both Indian and Malaysian dentists were not aware that oral analgesics can also be used to treat CTS (Figure 6). Marshal et al reported that steroid injections led to improvement of CTS symptoms but in our study only 3 -5% participants were aware of it [22]. Our results are similar to those reported by Alyousef et al, in which most of the participants agreed that CTS affects their job performance [21, 23]. But Indians are not aware that hypothyroidism people have a risk of emerging CTS.

The main limitation of this study is the low survey response rate, because it was carried out in small group. Second, because this was a pilot study, the inferential statistics may not fully reflect the populations of Indian and Malaysian dentists. More research is needed to confirm the current findings via patient examination (functional and clinical symptoms of CTS). A future study may be carried out among the dentists working in different specialties to find the stage of CTS that pertained to them.

Conclusions

Based on the data, both the community population had an adequate knowledge on CTS among dentists. Furthermore, there is a strong relation between CTS and rheumatoid arthritis. Dentists are more susceptible to CTS, hence they should take extra steps to avoid it. Increased awareness of the threat of CTS among dentists may help to reduce the risk of CTS, resulting in better quality of dental care. The successful management of CTS may be influenced by early detection of symptoms and education about occupational exposure. Early intervention is critical for dentists who are at a higher risk of acquiring CTS or are already experiencing its symptoms.

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None.

Conflicts of interest

None.

References

1. Burton C, Chesterton LS, Davenport G. Diagnosing and managing carpal tunnel syndrome in primary care. Br J Gen Pract [Internet]. 2014 May 1;64(622):262–3. Available from: http://bjgp.org/content/64/622/262.abstract
2. Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. Neurol Sci [Internet]. 2010 Jun 10;31(3):243–52. Available from: https://doi.org/10.1007/s10072-009-0213-9
3. American Academy of Orthopaedic Surgeons. Clinical Guideline on Diagnosis of Carpal Tunnel Syndrome [Internet]. American Academy of Orthopaedic Surgeons. 2007 [cited 2022 Aug 22]. Available from: https://www.aaos.org/aaos-now/2007/jul/clinical/clinical4/
4. Braddom RL. Physical Medicine & Rehabilitation. 3rd ed. Philadelphia: Elsevier Saunders; 2007. 1079–80 p.
5. Dorwart BB. Carpal tunnel syndrome: A review. Semin Arthritis Rheum [Internet]. 1984 Nov;14(2):134–40. Available from: https://www.sciencedirect.com/science/article/pii/0049017284900039
6. Krendel DA, Jobsis M, Gaskell PC, Sanders DB. The flick sign in carpal tunnel syndrome. J Neurol Neurosurg Psychiatry [Internet]. 1986 Feb 1;49(2):220–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3950646
7. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of Carpal Tunnel Syndrome in a General Population. JAMA [Internet]. 1999 Jul 14;282(2):153–8. Available from: https://doi.org/10.1001/jama.282.2.153
8. Phalen G. The carpal-tunnel syndrome. J Bone Jt Surg Am. 1966;48(A):380–3.
9. Phalen G. The carpal tunnel syndrome; seventeen years' experience in diagnosis and treatment of six hundred fifty-four hands. J Bone Jt Surg. 1966;48(A):211–28.
10. De Krom MCTFM, Knipschild PG, Kester ADM, Thijs CT, Boekkooi PF, Spaans F. Carpal tunnel syndrome: Prevalence in the general population. J Clin Epidemiol [Internet]. 1992;45(4):373–6. Available from: https://www.sciencedirect.com/science/article/pii/089543569290038O
11. Becker J, Nora DB, Gomes I, Stringari FF, Seitensus R, Panosso JS, et al. An evaluation of gender, obesity, age and diabetes mellitus as risk factors for carpal tunnel syndrome. Clin Neurophysiol [Internet]. 2002;113(9):1429–34. Available from: https://www.sciencedirect.com/science/article/pii/S1388245702002018
12. Ahmed AF, Mashael A, Fadwa A, Alanoud A, Bassam A, Emad M, et al. Prevalence of carpal tunnel syndrome symptoms among dentists working in Riyadh. Ann Saudi Med [Internet]. 2019 Mar 1;39(2):104–11. Available from: https://doi.org/10.5144/0256-4947.2019.07.03.1405
13. Leggat PA, Smith DR. Musculoskeletal disorders self-reported by dentists in Queensland, Australia. Aust Dent J [Internet]. 2006 Dec 1;51(4):324–7. Available from: https://doi.org/10.1111/j.1834-7819.2006.tb00451.x
14. Palmer KT. Carpal tunnel syndrome: The role of occupational factors. Best Pract Res Clin Rheumatol [Internet]. 2011;25(1):15–29. Available from: https://www.sciencedirect.com/science/article/pii/S1521694211000192
15. Haghighat A, Khosrawi S, Kelishadi A, Sajadieh S, Badrian H. Prevalence of clinical findings of carpal tunnel syndrome in Isfahanian dentists. Adv Biomed Res [Internet]. 2012;1:13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23210072
16. Alexopoulos EC, Stathi I-C, Charizani F. Prevalence of musculoskeletal disorders in dentists. BMC Musculoskelet Disord [Internet]. 2004;5(1):16. Available from: https://doi.org/10.1186/1471-2474-5-16
17. Leggat PA, Kedjarune U, Smith DR. Occupational Health Problems in Modern Dentistry: A Review. Ind Health [Internet]. 2007;45(5):611–21. Available from: https://www.jstage.jst.go.jp/article/indhealth/45/5/45_5_611/_article
18. Page MJ, O'Connor D, Pitt V, Massy-Westropp N. Exercise and mobilisation interventions for carpal tunnel syndrome. Cochrane Database Syst Rev [Internet]. 2012;(6). Available from: https://doi.org//10.1002/14651858.CD009899
19. Wellman H, Davis L, Punnett L, Dewey R. Work-related carpal tunnel syndrome (WR-CTS) in Massachusetts, 1992–1997: Source of WR-CTS, outcomes, and employer intervention practices. Am J Ind Med [Internet]. 2004 Feb 1;45(2):139–52. Available from: https://doi.org/10.1002/ajim.10326
20. Žídková V, Nakládalová M, Zapletalová J, Nakládal Z, Kollárová H. Experiences with preventing carpal tunnel syndrome in an automotive plant. Int J Occup Med Environ Health [Internet]. 2017;30(1):45–54. Available from: https://doi.org/10.13075/ijomeh.1896.00793
21. Alyousef YY, Alyousef FY, Almaymoni SM, Hazizi M, Almaymoni MM, Alyousef AY, et al. Awareness of carpal tunnel syndrome among adult population of Al Majmaah city, Saudi Arabia, 2018–2019. J Fam Med Prim Care [Internet]. 2019;8(10):3383. Available from: https://journals.lww.com/10.4103/jfmpc.jfmpc_400_18
22. Braun RM, Davidson K, Doehr S. Provocative testing in the diagnosis of dynamic carpal tunnel syndrome. J Hand Surg Am [Internet]. 1989;14(2, Part 1):195–7. Available from: https://www.sciencedirect.com/science/article/pii/0363502389900051
23. Stevens JC, Beard CM, O'Fallon WM, Kurland LT. Conditions Associated With Carpal Tunnel Syndrome. Mayo Clin Proc [Internet]. 1992;67(6):541–8. Available from: https://www.sciencedirect.com/science/article/pii/S0025619612604613

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RESEARCH ARTICLE

In the midst of imbalance: medical and healthcare students versus SARS-CoV-2

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Abstract

Background: During the COVID-19 era, it is crucial to determine the level of relevant infectious disease knowledge amongst medical students as they may influence public opinion by acting as informal medical advisors to their friends and family. We sought to assess the knowledge of students regarding COVID-19 at a single Polish medical university, to understand the level of knowledge and determine if dedicated COVID-19 education is necessary. **Material and methods:** The survey was conducted in Google Forms and access was obtained through the university's secure email. After exclusion, 1 001 students were enrolled. **Results:** The most common mask used amongst students is a surgical mask. Regarding SARS-CoV-2 transmission, 79.1% chose droplet and 19.3% chose airborne transmission. Only 35% agreed that surgical masks protect them from coronavirus and 70% strongly agreed or agreed that all healthcare workers should wear an N95/FFP3 mask. Students with a healthcare worker in the family more likely agreed that all healthcare workers should wear N95/FFP3 ($p = 0.001$). The source of information used affected the route of transmission chosen ($p = 0.006$). **Conclusions:** We recommend combating contradictory information by implementing dedicated education into the healthcare student curriculum on SARS-CoV-2, PPE, filtering efficiency of masks, modes of transmission of viruses, and how to use evidence-based medicine.

Keywords: students · vaccination · transmission · COVID-19 · masks

Citation

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TRANSPARENT PROCESS OPEN ACCESS

Introduction

Studies have shown that medical students are more willing to obtain the COVID-19 vaccine compared to non-medical students, possibly due to better health awareness [1]. During the pandemic, studies have shown that medical students have a high level of knowledge regarding COVID-19 and could help educate the general public [2-3]. According to a study from the UK, the portrayal of COVID-19 safety measures has been inaccurate. Instead of highlighting the resilience of students and young people even in the absence of support, headlines remained about the few individuals that engaged in risky behaviors despite a raging pandemic [4]. We wanted to determine how knowledgeable medical students are amidst the COVID-19 pandemic and their approach to COVID-19 safety.

Despite the rapid increase of published medical articles regarding COVID-19 [5], virus transmission and protection remain unclear, which is why more research is needed to guide public health [6]. Widespread access to the internet and social media led to the quick dissemination of fake news about the new coronavirus (SARS-CoV-2). Unfortunately, not only anonymous members of society spread disinformation, but also public figures that were believed to be reliable [7]. Commonly implemented face mask mandates raised concerns about mask safety and efficacy. Comfort (physical and psychological), cost, insufficient efficacy with improper usage are only some arguments mentioned against wearing a mask [8]. Another problem is the anti-vaccine movement. Very rare, but life-threatening adverse effects of vaccines are constantly mentioned [9].

Medical students may have more time than practicing physicians to stay up-to-date with current medical guidelines and new research studies. Medical students may also be more aware of effective public health measures and basic hygiene to control COVID-19. We sought to determine the medical students' level of knowledge about infectious diseases and COVID-19. By doing so, one can gauge how well medical information about COVID-19 is being disseminated and understood. Moreover, it may encourage medical schools to augment their curriculum by emphasizing relevant public health and infectious disease principles to their students.

Material and methods

The survey aiming to investigate healthcare students' knowledge about SARS-CoV-2 safety and approaches was designed through a discussion amongst the co-authors. The final version was reviewed and accepted by final-year medical students (n = 4) and neurosurgery specialists guiding this research project (n = 2). The final version of the questionnaire consisted of a total of 36 questions. The first 8 questions consisted of single choice questions regarding demographic data (sex, age, residence, study language, year of studies, exposure to healthcare environments, family in healthcare). Furthermore, 11 questions consisted of the most common types of masks worn, safety measures used, route of transmission, testing positive for COVID-19, vaccination and vaccine efficacy [10]. Next, there were 15 Likert scale statements with answers ranging from: strongly disagree, disagree, I don't know, agree, strongly agree. Lastly, 2 questions asked about the main sources of information. The survey was conducted by using Google Forms and the link to the survey was sent out through the University's secure email system. The link was also shared on the English Division Medical student pages on Facebook, therefore using the snowball sampling method. The survey was sent out from January 18th to March 31st 2021.

The statistical analysis was performed using an R software package version 4.1.0. Single choice questions were analyzed using frequency tables and the chi-squared test. Due to the small number of specific groups in some conditions, the p-value is based on the Monte Carlo approach.

Results

The general demographics of the participants are described in Table 1. The results of single or multiple-choice questions can be seen in Table 2. The most significant 5-point Likert scale questions can be seen in Figure 1, along with the following descriptions of the remainder. Face shields are not considered good enough at protecting yourself from coronavirus by 86.21% of participants. Avoiding high-risk situations and crowded environments are implemented by 72.83% of respondents. 36.46% of respondents stated that they do not know if taking supplements such as vitamin D and vitamin C every day may be used as prophylaxis or treatment of COVID-19. 55.54% agreed or strongly agreed with the statement that they take supplements such as vitamin D, vitamin C, B complex, and/or zinc every day. 65.73% strongly agreed and agreed that in the past month, they have felt uncomfortable not wearing a mask when around others. 65.93% agreed and strongly agreed that other factors such as humidity and temperature affect virus transmission.

The most common mask used outside and indoors by both groups was a surgical mask, but participants with relatives in the medical field more frequently chose KN95, FFP2, and FFP3 masks. Participants without relatives in medical fields rather chose scarves, bandanas, or other fabric masks. Participants with relatives in medical fields agreed or strongly agreed with the statement that "All health care workers should wear N95/FFP3 masks," while those without relatives in the medical field tended to have no opinion or more frequently disagreed with the statement.

Table 1. General demographics and divisions of participants

Language	
English	310 (30.97%)
Polish	655 (65.43%)
Age groups	
< 19	72 (7.19%)
20-29	896 (89.51%)
30-39	26 (2.59%)
Nationality/Country of origin	
Poland	715 (71.43%)
Sweden	93 (9.23%)
Norway	73 (7.29%)
Experience within the medical field in the past 6 months	
None	531 (53.04%)
Internal medicine	177 (17.68%)
Outpatient setting	68 (6.79%)
Does someone in your family work in the medical field?	
Yes	463 (46.25%)
No	538 (53.75%)

Table 2. Single or multiple choice questions

Type of facial mask worn inside	
Surgical masks	574 (57.34%)
Fabric mask (with or without filter)	166 (16.58%)
KN95	88 (8.79%)
FFP2	77 (7.69%)
N95	32 (3.20%)
FFP3	21 (2.10%)
Main route of transmission	
Droplet transmission	792 (79.12%)
Airborne transmission	193 (19.28%)
What do you do before applying your mask?	
Nothing	453 (45.25%)
Use hand sanitizer	241 (24.08%)
Wash hands with soap and water	294 (29.37%)
How do you store your masks?	
Pocket of jacket	290 (28.97%)
Throw away after each use	225 (22.48%)
Purse/ backpack	144 (14.39%)

Do you dispose of your masks?	
Dispose after 1 use	378 (37.76%)
Dispose after multiple uses	308 (30.77%)
Rotate masks	242 (24.18%)
Difficulties with mask use	
Glasses fog up	370 (36.97%)
Acne outbreaks	163 (16.28%)
Pain behind ears	153 (15.28%)
Feeling that you cannot breathe	119 (11.89%)
Why do you wear a mask?	
To protect myself and others	712 (71.12%)
To protect others	158 (15.79%)
Because it is currently required by the law	106 (10.59%)
Did you test positive for SARS-CoV-2?	
Yes	97 (9.69%)
No	904 (90.31%)
Have any of your family members or friends tested positive for SARS-CoV-2?	
Yes	683 (68.23%)
No	318 (31.76%)

Table 2. cd

Did you or will you receive the COVID vaccine?	
Yes, I already received the vaccine (1st dose or both)	665 (66.43%)
Not yet, but I am waiting to receive it	251 (25.07%)
No, I do not plan on it	85 (8.50%)
Main source of information about SARS-CoV-2 safety	
WHO	453 (45.25%)
Research papers	161 (16.08%)
Doctors	124 (12.39%)
Government websites	100 (9.99%)
CDC	90 (8.99%)

Participants with relatives in medical fields differed from participants without relatives in medical fields in their responses to questions about COVID-19 protection which can be seen in Table 3.

Table 3. The differences between responses of participants with and without relatives in the medical field

Question	χ^2 statistics
What type of facial protection do you wear outside (most commonly)?	20.911*
What type of facial protection do you wear indoors when around others (most commonly)? If you are a healthcare worker, what mask do you wear at work?	32.939***
The main route of transmission of the coronavirus is?	1.7452
All health care workers should wear N95/FFP3 masks	12.599**
Wearing a surgical mask is good enough to protect me from the coronavirus	2.8653
Other factors such as humidity and temperature affect virus transmission	0.22241

*p < 0.05; **p < 0.01; ***p < 0.001

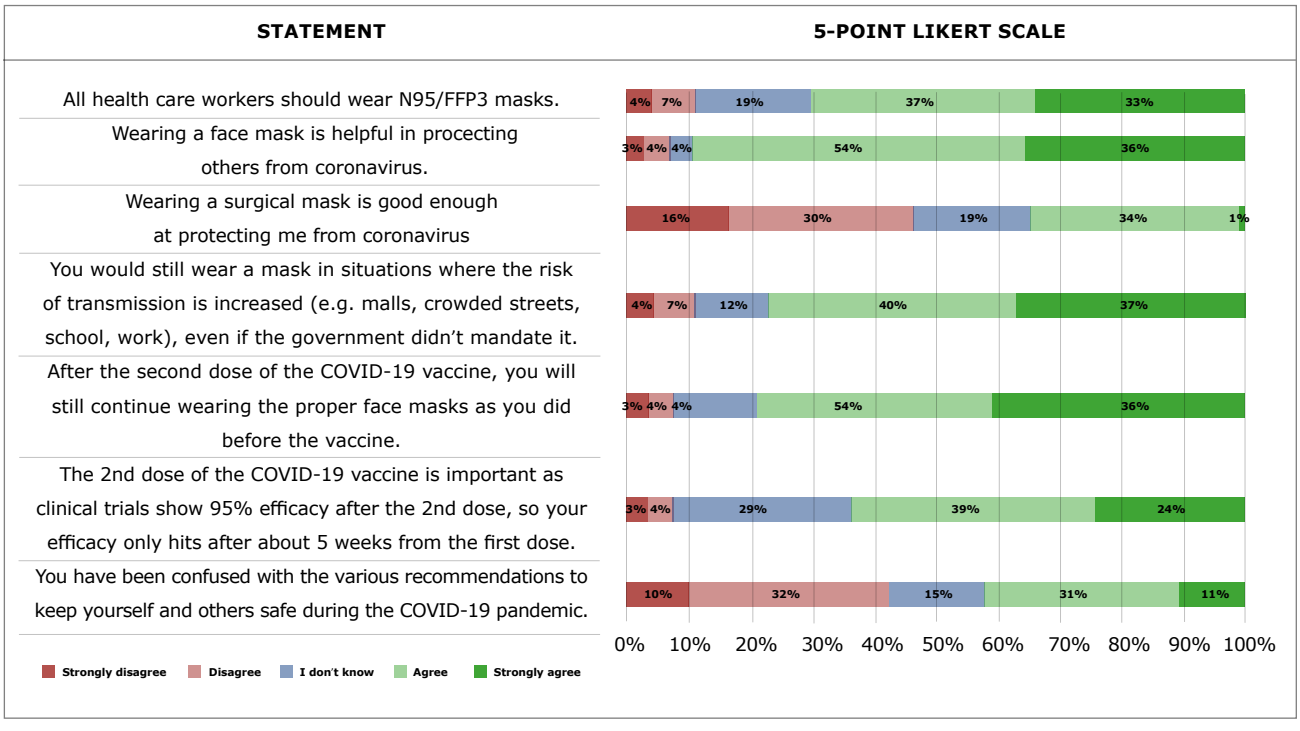

Figure 1. Likert scale figure

Students most commonly wore surgical masks indoors and outside, but students who studied in the Polish language more frequently had chosen fabric masks with or without filters as their second choice – Table 4.

Table 5 shows the significance of the main route of transmission chosen on the other questions. There were no significant differences between the chosen main route of transmission and the opinion about efficiency of surgical masks, however the participants who chose droplets as a main route of transmission, more frequently agreed with the sentence that all healthcare workers should wear N95/FFP3 masks than participants who had chosen an airborne route of transmission. The choice of the main route of transmission of SARS-CoV-2 did not affect the understanding of humidity and temperature on transmission ($p = 0.596$). Even though proportions of main sources of information about the transmission of SARS-CoV-2 were similar, the participants who had chosen the droplet route as the main route, significantly more frequently had pointed to World Health Organization (WHO) and research papers as their main source than people who had chosen the airborne route.

Table 4. The differences between the responses of students studying in English and Polish

Question	χ^2 statistics
What type of facial protection do you wear outside (most commonly)?	33.665***
What type of facial protection do you wear indoors when around others (most commonly)? If you are a healthcare worker, what mask do you wear at work?	90.439***
The main route of transmission of the coronavirus is?	51.028***

*p < 0.05; **p < 0.01; ***p < 0.001

Table 5. Selected differences between different routes of transmission

Question	χ^2 statistics
Transmission → Humidity/temperature	11.859
Transmission → All health care workers should wear N95/FFP3 masks	60.089***
Transmission → Wearing a surgical mask is good enough at protecting me from coronavirus	14.998
Transmission → Source	173.51**

*p < 0.05; **p < 0.01; ***p < 0.001

Discussion

Amid an imbalance between COVID-19 recommendations, it is crucial to find reliable sources of information and examples of role models to follow in society. In our study, we wanted to find out whether medical students' knowledge about SARS-CoV-2 protection is as up-to-date as currently possible, if there are deficiencies in knowledge and if the current generation of healthcare students could potentially be reliable role models for communities in the future. It appears that parts of society started to undermine government recommendations possibly due to facing constant changes (to wear or not to wear masks) within a country as well as in neighboring countries. There are also different opinions about if to wear or not to wear a mask when fully vaccinated due to the delta strain. The inconsistencies between government recommendations can lead to a growing mistrust towards current and forthcoming government recommendations. Recent studies show that higher levels of conspiracy thinking were associated with less adherence to government recommendations or willingness to get vaccinated [11].

Type of masks and the understanding of the transmission of SARS-CoV-2 amongst healthcare students

The debate on the mode of transmission of SARS-CoV-2 is ongoing and far from concluded. We recognize that medical students are not expected to know the definite main route of transmission of SARS-CoV-2, but we sought to determine what they think based on their medical knowledge of other viruses. According to the article by Greenhalgh et al, the dominant route of SARS-CoV-2 is airborne [12]. Interestingly, although most participants stated that droplet transmission is the main route of transmission, around 20% chose airborne transmission. Students must learn to practice medicine based on new research, instead of relying on general opinions. Surprisingly, nearly half of the participants disagreed that surgical masks are effective in protecting themselves from the novel coronavirus even though most participants chose the droplet route of transmission. To enable students to learn and thrive during the pandemic, we believe they should always feel protected. Although most participants chose droplet transmission and most chose that

they wear surgical masks most commonly, the majority still agreed that all healthcare workers should wear N95/FFP3 masks. This leads to questions about why most of the respondents think all healthcare workers should wear masks with higher filtering efficiency and if made available, would most medical students choose to wear them?

Interestingly, the participants that chose airborne transmission were less likely to agree that all healthcare workers should wear N95-type masks ($p = 0.001$). This may have been due to participants that chose airborne transmission knew the importance of higher filtering efficiency masks and the shortage of personal protection equipment (PPE) in settings with the highest risk of transmission, e.g. COVID-intensive care units. Results from an appraisal study showed that the healthcare workers' major concern was running out of PPE [13]. Although not statistically significant, fabric or cloth masks were the second most common masks worn amongst students, despite the fact that cloth masks are not worn in operating rooms and there is a lack of evidence of their efficacy [14-15]. It is important to note that the participants who stated they have a healthcare worker in the family, chose different masks than those who did not ($p \leq 0.001$). Students without family members in healthcare chose lesser filtering efficiency masks. Students with families in healthcare may have been exposed to more studies and personal experiences with COVID-19 leading to their precautions. Students need to understand what filtering efficiency and PPE is necessary to protect themselves according to the mode of transmission and size of viruses. Additionally, if there is a lack of PPE, students should be taught how to best replicate PPE conditions with available materials and understand that the quality of masks matters for their protection.

The questionnaire did not include 'aerosolized particles' among the answer choices, to determine if there would be considerable contrast between answers with fewer choices. Droplets are not present in the air for long periods and instead, they convert into bioaerosol residues which could then remain in the air for extended periods [16]. When droplets evaporate, they become "droplet nuclei" which are dried-up particles that contain viruses that can remain airborne and can be widely dispersed over an extensive area [17]. The rate of evaporation is directly related to ambient humidity and temperature and the dispersion of droplet nuclei does depend on ambient conditions [17]. As described by Borak, hotter and more humid environments lead to less dispersion of virus-containing particles [17]. Most healthcare students agreed that other factors such as humidity and temperature affect virus transmission, although this knowledge did not affect their choices of the route of transmission. Educating medical students on the possible routes, conditions, and detailed mechanisms of transmission of viral particles will be crucial for the next generation of medical doctors to stay safe.

Harvey explained the next generation of medical students will need to be able to deal with future pandemics and will live in a world of PPE and the fears of aerosolized dangers. He explained that students may have been told to stay home for their protection and possibly due to the PPE shortage [18]. Most participants agreed that in the past month, they have felt uncomfortable not wearing a mask when around others. Knowledge may alleviate these discomforts. Educating future physicians is crucial in filling in gaps between healthcare demand and access to care and even more so during a pandemic [19]. It was described that the non-essential label should not discourage students, but rather reflect a necessary safety precaution [19]. One of the roles of medical students during the COVID-19 pandemic involved educating peers online. Studies concluded that due to a medical student's knowledge base, during restricted clinical duties, students could serve as a voice of leadership to non-medical peers [19].

Are medical students and students of healthcare fields good examples for the public to follow?

While face shields are useful as an additional protective measure, they are not good at protecting others due to the expelled droplets that can spread easily [20]. Almost all participants agreed that face shields alone would not protect one from SARS-CoV-2. The face shield could be related to plexiglass used in supermarkets because both are used as a barrier. Large droplets could be blocked, but barriers such as these would not be effective for aerosolized particles [21]. High-quality cloth masks or surgical masks are preferred over masks with exhalation valves to minimize SARS-CoV-2 spread [22]. Our survey participants acknowledged the need to protect others with the use of proper face masks during a time when few were vaccinated.

Despite the Center for Disease Control (CDC) recommendations, not all national governments mandated wearing face masks in public places. On the other hand, in some countries the law required mask use even outdoors. The efficacy of cloth masks in the prevention of infection transmission is quite limited [23] and there has been a constant debate about universal mask use since the COVID-19 pandemic outbreak [24]. The majority of our respondents agreed that they would wear masks in high-risk situations even without a government mandate, which together with social distancing and avoiding high-risk environments are considered to be crucial in controlling the coronavirus spread [24-25]. The willingness to wear a mask without a mandate in high-risk situations signifies the understanding of viral spread by students.

Apart from universal knowledge about SARS-CoV-2 infection prevention which includes wearing a mask, avoiding close contacts, and washing hands [25], alternative approaches with food supplements are widely discussed. Taking vitamin C during the winter months, especially while having cold symptoms is a common practice. In the light of

common cold prophylaxis and treatment with zinc [26-27] or vitamin C [28,29], we wanted to determine whether our respondents were using an analogous approach against SARS-CoV-2 infection. This could be relevant to our study population since many adults in Poland are vitamin D deficient [30]. However, a recent study by Li et al. observed no association between low vitamin D levels and SARS-CoV-2 seropositivity after adjusting for potential cofounders [31]. In a randomized control trial Murai et al. measured the efficacy of a single high dose of vitamin D3 on COVID-19 patients' duration of hospital stay. In comparison with placebo, there was no significant reduction in days of hospital stay [32]. Current coronavirus prevention guidelines do not recommend any pharmacological prophylaxis due to the lack of data supporting its efficacy [33]. Some studies have proven antiviral, anti-inflammatory, and antioxidant effects of several food supplements [34-36], however, it is worth noting that potential laboratory effects may not be clinically relevant. These disagreements most likely led to the hesitancy of our respondents when answering questions about taking supplements as possible prophylaxis or treatment of COVID-19. Their responses resembled what was available in the literature at the time and signifies that they could be role models for the public to learn from. Additionally, students could help in answering common misconceptions about dietary supplementation for COVID-19 infection.

Are medical students and health science students good examples for post-vaccine public health protection?

Although 90% of respondents never tested positive for SARS-CoV-2, there was still a high amount of positive cases among their close family members and friends. Almost half of the participants had someone in their family that works in the medical field. This confirms the importance of awareness of safety measures in this specific group. Previous studies have shown [37] that more than 90% of medical students are aware, but only have a superficial understanding of the disease's etiology, currently known modes of transmission, primary symptoms and risk perception. There is a need to improve student awareness about safety measures to strengthen the possible pivotal role students can play in public health awareness about the SARS-CoV-2 [2, 19, 37]. Most participants knew that the 2nd dose of an mRNA vaccination series is important to reach maximum vaccine efficacy. The high willingness to get vaccinated against SARS-CoV-2 amongst students is yet another affirmation of the possibility of students being on the frontline of combating SARS-CoV-2 misinformation. The poor attitude of the general population towards vaccination is mainly due to the mistrust of vaccine benefits and concerns about its adverse effects. Healthcare students can be a great resource for the general population's doubts about the vaccine. Students should be up-to-date on new publications that could impact the public's health decisions and could reduce vaccine hesitancy. Students should be taught how to define vaccine risks and benefits.

General problems found amongst students and approaches to public health

The most common primary source of information about face masks and COVID-19 safety was the WHO, research papers and doctors. Surprisingly, research papers were not the most common source amongst students. The source of information that participants chose had a significant effect on their answer to the questions about the main route of transmission ($p=0.006$). Although participants used various sources, the most commonly chosen route of transmission remained the same amongst groups. In a study about what the world expects from the WHO, there were multiple deficiencies of the WHO listed along with recommendations for improvement [38]. Precautions can be taken only when national bodies responsible for epidemic control agree and recognize the importance of the route of transmission which can then lead to appropriate actions [39]. Mask protection and filtering efficiency should also be topics that medical students are taught and truly understand.

Due to the delta variant, the newest WHO recommendation [40] for fully vaccinated people is to continue wearing face masks. Our study group reflected these recommendations with the high interest of our respondents in choosing to continue wearing proper face masks post-vaccination. However, caution should be drawn from this conclusion due to the time frame; at the time of vaccinating these medical students, most of the general public was not vaccinated yet. When new mutations were discovered, their impact was unknown [41]. At the time (as of July 1st 2021), 57,1% of the population of Israel was fully vaccinated [42]. Due to the national vaccination campaign, Israel became a role model for other countries regarding an efficient vaccination process. Now, the world is looking at the situation in Israel with fear due to the new COVID-19 delta variant, which was proven to infect some fully vaccinated adults [43-44]. With rising daily coronavirus infection rates, Israel has reimposed the requirement of wearing masks indoors for everyone [45-46], while the WHO has also recommended that fully vaccinated people continue wearing masks. This may be the reason for contradictory information between WHO and CDC recommendations. It is noteworthy that according to a recent study the Pfizer-BioNTech's tozinameran vaccine (in Europe marketed as Comirnaty®) vaccine has a minimal decrease in effectiveness (about a 5,5% decrease) against the new delta variant [47]. Interestingly, the WHO's recommendations do not match the CDC's recommendations for fully vaccinated people at the moment. According to the CDC's newest public health recommendations, resuming most activities for fully vaccinated people

without wearing masks is recommended [48]. Fully vaccinated people also do not need COVID-testing after exposure and before or after travel. Fully vaccinated people also do not need to self-quarantine, which is different from the current WHO recommendations [48-49]. Students should be taught how to interpret recommendations because such discrepancies can be very distressing, particularly to those who are paying close attention to the pandemic. Students should be informed on how to interpret studies about new virus variants to be able to determine risks for themselves and their future patients.

Pre-pandemic studies have found that there is a decline in empathy possibly due to the increase of psychological stress in medical school and residency which can further compromise professionalism and can threaten the quality of healthcare [50]. Lack of balance was mentioned as the main stressor for medical students [51]. The constantly changing COVID restrictions and schedules for students would not be defined as consistent. Studies determined it will be important to study the extent of student adaptation during the COVID-19 pandemic and its effect on medical education overall [52]. With more adequate availability of PPE, medical students should be allowed back to the bedside to learn valuable lessons from frontline survivors [53]. Medical schools can consider adding virtual credits for students taking part in scientific writing and continuing student engagement whenever possible [53]. Studies have shown that COVID-19 had the greatest effect on students' confidence and preparedness to jump from student to doctor [54]. Barriers to critical thinking have been described amongst medical students with obedience to the system being one of the contributing factors [55]. Anxiety, stress, and fatigue were shown to prevent critical focus and thinking [55]. It is important to prioritize teaching medical students to filter out what the media and news intensify and focus on evidence-based medicine. Students must be included in medical education so that when they finish their studies, they can continue to support public health while having the psychological strength to do so.

There was a bias of more female respondents and participants from the Polish division. Response bias may be present due to healthcare and medical students' desirable answers to topics that are perceived as sensitive such as health behaviors and safety [56-57]. Nonetheless, responses varied and not all participants chose desirable answers to controversial statements like government mandates and avoiding high-risk situations. Caution should be taken when drawing conclusions from this study due to the time frame the survey was administered. At the time of the survey, (January 18th – March 31st 2021) the post-vaccination time frame for most students was during a time when most of the general population was still not vaccinated.

Conclusions

Medical and healthcare students have the potential to be even better role models for the general public to follow. Students had a high willingness to get vaccinated and the majority knew the importance of the 2nd dose of an mRNA series in reaching maximum efficacy. There is a need to educate students on the filtering efficiency of masks and what PPE is necessary according to the mode of transmission and size of viruses. Although most participants stated that droplet is the route of SARS-CoV-2 transmission and most marked that they wear surgical masks most commonly, they didn't believe surgical masks protect them and stated that all healthcare workers should wear N95/FFP3 masks. Students should be informed on how to find appropriate sources of information and how to interpret studies about new virus variants to be able to determine risks for themselves and their future patients.

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References

1. Szmyd B, Bartoszek A, Karuga FF, Staniecka K, Błaszczyk M, Radek M. Medical Students and SARS-CoV-2 Vaccination: Attitude and Behaviors. Vaccines [Internet]. 2021 Feb 5;9(2):128. Available from: https://www.mdpi.com/2076-393X/9/2/128
2. Alsoghair M, Almazyad M, Alburaykan T, Alsultan A, Alnughaymishi A, Almazyad S, et al. Medical Students and COVID-19: Knowledge, Preventive Behaviors, and Risk Perception. Int J Environ Res Public Health [Internet]. 2021 Jan 19;18(2):842. Available from: https://www.mdpi.com/1660-4601/18/2/842

3. Matusiak Ł, Szepietowska M, Krajewski P, Białynicki-Birula R, Szepietowski J. Face masks use during the COVID-19 pandemic: Differences in attitudes and practices between medical and non-medical students. A survey of 2256 students in Poland. Adv Clin Exp Med [Internet]. 2020 Oct 30;29(10):1201–3. Available from: http://www.advances.umed.wroc.pl/pdf/2020/29/10/1201.pdf
4. Reicher S, Drury J. Pandemic fatigue? How adherence to covid-19 regulations has been misrepresented and why it matters. BMJ [Internet]. 2021 Jan 18;372:n137. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.n137
5. Chen Q, Allot A, Lu Z. LitCovid: an open database of COVID-19 literature. Nucleic Acids Res [Internet]. 2021 Jan 8;49(D1):D1534–40. Available from: https://academic.oup.com/nar/article/49/D1/D1534/5964074
6. The Lancet Respiratory Medicine. COVID-19 transmission – up in the air. Lancet Respir Med [Internet]. 2020 Dec;8(12):1159. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260020305142
7. Orso D, Federici N, Copetti R, Vetrugno L, Bove T. Infodemic and the spread of fake news in the COVID-19-era. Eur J Emerg Med [Internet]. 2020 Oct 23;27(5):327–8. Available from: https://journals.lww.com/10.1097/MEJ.0000000000000713
8. Matuschek C, Moll F, Fangerau H, Fischer JC, Zänker K, van Griensven M, et al. Face masks: benefits and risks during the COVID-19 crisis. Eur J Med Res [Internet]. 2020 Dec 12;25(1):32. Available from: https://eurjmedres.biomedcentral.com/articles/10.1186/s40001-020-00430-5
9. Hotez P. COVID vaccines: time to confront anti-vax aggression. Nature [Internet]. 2021 Apr 29;592(7856):661–661. Available from: http://www.nature.com/articles/d41586-021-01084-x
10. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med [Internet]. 2020 Dec 31;383(27):2603–15. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2034577
11. Freeman D, Waite F, Rosebrock L, Petit A, Causier C, East A, et al. Coronavirus conspiracy beliefs, mistrust, and compliance with government guidelines in England. Psychol Med [Internet]. 2022 Jan 21;52(2):251–63. Available from: https://www.cambridge.org/core/product/identifier/S0033291720001890/type/journal_article
12. Greenhalgh T, Jimenez JL, Prather KA, Tufekci Z, Fisman D, Schooley R. Ten scientific reasons in support of airborne transmission of SARS-CoV-2. Lancet. 2021 May;397(10285):1603–5.
13. Hoernke K, Djellouli N, Andrews L, Lewis-Jackson S, Manby L, Martin S, et al. Frontline healthcare workers' experiences with personal protective equipment during the COVID-19 pandemic in the UK: a rapid qualitative appraisal. BMJ Open [Internet]. 2021 Jan 20;11(1):e046199. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2020-046199
14. Chughtai AA, Seale H, Macintyre CR. Effectiveness of Cloth Masks for Protection Against Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis [Internet]. 2020 Oct;26(10). Available from: http://wwwnc.cdc.gov/eid/article/26/10/20-0948_article.htm
15. Chughtai AA, Seale H, MacIntyre CR. Use of cloth masks in the practice of infection control – evidence and policy gaps. Int J Infect Control [Internet]. 2013 Jun;9(3):3. Available from: https://www.ijic.info/article/view/11366
16. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res [Internet]. 2020 Sep;188:109819. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0013935120307143
17. Borak J. Airborne Transmission of COVID-19. Occup Med (Chic Ill) [Internet]. 2020 Jul 17;70(5):297–9. Available from: https://academic.oup.com/occmed/article/70/5/297/5849370
18. Harvey EJ. A lost cohort of medical students. Can J Surg [Internet]. 2020 Oct 1;63(5):E489–E489. Available from: http://www.canjsurg.ca/lookup/doi/10.1503/cjs.020620
19. Patrinely JR, Zakria D, Berkowitz ST, Johnson DB, Totten DJ. COVID-19: the Emerging Role of Medical Student Involvement. Med Sci Educ [Internet]. 2020 Dec 12;30(4):1641–3. Available from: https://link.springer.com/10.1007/s40670-020-01052-6
20. Khan MM, Parab SR. Safety Guidelines for Sterility of Face Shields During COVID 19 Pandemic. Indian J Otolaryngol Head Neck Surg [Internet]. 2021 Mar 30;73(1):85–6. Available from: https://link.springer.com/10.1007/s12070-020-01865-2
21. Pilkington BC, Wilkins V, Nichols DB. Educating ethically during COVID-19. Int J Ethics Educ [Internet]. 2021 Apr 29;6(1):177–93. Available from: http://link.springer.com/10.1007/s40889-021-00120-8
22. Verma S, Dhanak M, Frankenfield J. Visualizing droplet dispersal for face shields and masks with exhalation valves. Phys Fluids [Internet]. 2020 Sep 1;32(9):091701. Available from: http://aip.scitation.org/doi/10.1063/5.0022968
23. Sharma S, Mishra M, Mudgal S. Efficacy of cloth face mask in prevention of novel coronavirus infection transmission: A systematic review and meta-analysis. J Educ Health Promot [Internet]. 2020 Jul;9(1):192. Available from: http://www.jehp.net/text.asp?2020/9/1/192/290942

24. Tirupathi R, Bharathidasan K, Palabindala V, Salim SA, Al-Tawfiq JA. Comprehensive review of mask utility and challenges during the COVID-19 pandemic. Le Infez Med [Internet]. 2020 Jun 1;28(suppl 1):57–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32532940
25. How to Protect Yourself & Others | CDC [Internet]. 2022 [cited 2022 Aug 10]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html
26. Al-Nakib W, Higgins PG, Barrow I, Batstone G, Tyrrell DAJ. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother [Internet]. 1987 Dec;20(6):893–901. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/20.6.893
27. Science M, Johnstone J, Roth DE, Guyatt G, Loeb M. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. Can Med Assoc J [Internet]. 2012 Jul 10;184(10):E551–61. Available from: http://www.cmaj.ca/lookup/doi/10.1503/cmaj.111990
28. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr [Internet]. 2006 Jan 1;60(1):9–17. Available from: https://www.nature.com/articles/1602261
29. Johnston C, Barkyoumb G, Schumacher S. Vitamin C Supplementation Slightly Improves Physical Activity Levels and Reduces Cold Incidence in Men with Marginal Vitamin C Status: A Randomized Controlled Trial. Nutrients [Internet]. 2014 Jul 9;6(7):2572–83. Available from: http://www.mdpi.com/2072-6643/6/7/2572
30. Płudowski P, Ducki C, Konstantynowicz J, Jaworski M. Vitamin D status in Poland. Polish Arch Intern Med [Internet]. 2016 Aug 9;126(7–8):530–9. Available from: http://pamw.pl/en/node/3479
31. Li Y, Tong CH, Bare LA, Devlin JJ. Assessment of the Association of Vitamin D Level With SARS-CoV-2 Seropositivity Among Working-Age Adults. JAMA Netw Open [Internet]. 2021 May 19;4(5):e2111634. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779952
32. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D 3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19. JAMA [Internet]. 2021 Mar 16;325(11):1053. Available from: https://jamanetwork.com/journals/jama/fullarticle/2776738
33. Adams KK, Baker WL, Sobieraj DM. Myth Busters: Dietary Supplements and COVID-19. Ann Pharmacother [Internet]. 2020 Aug 12;54(8):820–6. Available from: http://journals.sagepub.com/doi/10.1177/1060028020928052
34. Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra P V. Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol [Internet]. 2020 Oct 7;11:2337. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2020.570122/full
35. Sahebnasagh A, Saghafi F, Avan R, Khoshi A, Khataminia M, Safdari M, et al. The prophylaxis and treatment potential of supplements for COVID-19. Eur J Pharmacol [Internet]. 2020 Nov;887:173530. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299920306221
36. Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas [Internet]. 2021 Jan;143:1–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378512220303467
37. Ikhaq A, Bint E Riaz H, Bashir I, Ijaz F. Awareness and Attitude of Undergraduate Medical Students towards 2019-novel Corona virus. Pakistan J Med Sci [Internet]. 2020 May 18;36(COVID19-S4):S32. Available from: https://www.pjms.org.pk/index.php/pjms/article/view/2636
38. Kuznetsova L. COVID-19: The World Community Expects the World Health Organization to Play a Stronger Leadership and Coordination Role in Pandemics Control. Front Public Heal [Internet]. 2020 Sep 8;8:470. Available from: https://www.frontiersin.org/article/10.3389/fpubh.2020.00470/full
39. Morawska L, Cao J. Airborne transmission of SARS-CoV-2: The world should face the reality. Environ Int [Internet]. 2020 Jun;139:105730. Available from: https://linkinghub.elsevier.com/retrieve/pii/S016041202031254X
40. Coronavirus disease (COVID-19) [Internet]. Geneva; 2020. Available from: https://apps.who.int/iris/handle/10665/334383
41. Grubaugh ND, Hanage WP, Rasmussen AL. Making Sense of Mutation: What D614G Means for the COVID-19 Pandemic Remains Unclear. Cell [Internet]. 2020 Aug;182(4):794–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867420308175
42. Coronavirus (COVID-19) Vaccinations - Statistics and Research / Our World in Data [Internet]. 2021 [cited 2021 Oct 12]. Available from: https://ourworldindata.org/covid-vaccinations?country=JPN~USA
43. Lieber D. Delta Variant Outbreak in Israel Infects Some Vaccinated Adults. Wall Str J [Internet]. 2021; Available from: https://www.wsj.com/articles/vaccinated-people-account-for-half-of-new-covid-19-delta-cases-in-israeli-outbreak-11624624326

44. Hendrix S. Israel says vaccine protecting it against delta variant. Washington Post [Internet]. 2021; Available from: https://www.washingtonpost.com/world/middle_east/israel-delta-vaccine-shield-holding/2021/06/28/1ba865b2-d7e1-11eb-8c87-ad6f27918c78_story.html
45. Coronavirus: Israel races to vaccinate children as Delta variant cases swell South [Internet]. China Morning Post. 2021 [cited 2021 Oct 12]. Available from: https://www.scmp.com/news/world/middle-east/article/3139463/coronavirus-israel-races-vaccinate-children-delta-variant?module=perpetual_scroll_0&pgtype=article&campaign=3139463
46. Staff T. Bennett: Young people must get vaccinated to avoid reinstatement of restrictions [Internet]. Times of Israel. 2021 [cited 2021 Oct 12]. Available from: https://www.timesofisrael.com/cases-rise-but-hospitalizations-remain-low-as-coronavirus-cabinet-set-to-meet/
47. Bernal JL, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med [Internet]. 2021 Aug 12;385(7):585–94. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2108891
48. Interim Public Health Recommendations for Fully Vaccinated People [Internet]. CDC. 2021 [cited 2021 Oct 22]. Available from: https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/grc-747228?lang=en
49. Episode #23 - I am vaccinated, what next? [Internet]. WHO. 2021 [cited 2021 Oct 12]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5/episode-23---i-am-vaccinated-what-next
50. Neumann M, Edelhäuser F, Tauschel D, Fischer MR, Wirtz M, Woopen C, et al. Empathy Decline and Its Reasons: A Systematic Review of Studies With Medical Students and Residents. Acad Med [Internet]. 2011 Aug;86(8):996–1009. Available from: http://journals.lww.com/00001888-201108000-00024
51. Hill MR, Goicochea S, Merlo LJ. In their own words: stressors facing medical students in the millennial generation. Med Educ Online [Internet]. 2018 Jan 5;23(1):1530558. Available from: https://www.tandfonline.com/doi/full/10.1080/10872981.2018.1530558
52. Ferrel MN, Ryan JJ. The Impact of COVID-19 on Medical Education. Cureus [Internet]. 2020 Mar 31;12(3). Available from: https://www.cureus.com/articles/29902-the-impact-of-covid-19-on-medical-education
53. Chandratre S. Medical Students and COVID-19: Challenges and Supportive Strategies. J Med Educ Curric Dev [Internet]. 2020 Jan 24;7:238212052093505. Available from: http://journals.sagepub.com/doi/10.1177/2382120520935059
54. Choi B, Jegatheeswaran L, Minocha A, Alhilani M, Nakhoul M, Mutengesa E. The impact of the COVID-19 pandemic on final year medical students in the United Kingdom: a national survey. BMC Med Educ [Internet]. 2020 Dec 29;20(1):206. Available from: https://bmcmededuc.biomedcentral.com/articles/10.1186/s12909-020-02117-1
55. Kasalaei A, Amini M, Nabeiei P, Bazrafkan L, Mousavinezhad H. Barriers of Critical Thinking in Medical Students' Curriculum from the Viewpoint of Medical Education Experts: A Qualitative Study. J Adv Med Educ Prof [Internet]. 2020 Apr;8(2):72–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32426391

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REVIEW ARTICLE

Advantages, limitations and new perspectives on the implantation of subcutaneous cardioverter-defibrillator

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Abstract

Subcutaneous cardioveter-defibrillator (S-ICD) gained considerable place in sudden cardiac death (SCD) prevention. The main advantage of this device is the possiblility of implantating it outside of blood vessel. The lack of permanent pacing and antitachycardia pacing (ATP) are its key limitations. New research is focused on creating an extravessel device that could combine the role of cardioverter and pacemaker. The main difficulty is the mutual interference of sensing.

Keywords: subcutenous cardioverter-defibrillator (S-ICD) · ventricular pacing · sudden cardiac death

Citation

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Introduction

Sudden cardiac death (SCD) in the course of ventricular arrythmias is the cause of 20% of deaths in Western countries [1]. In 2012 the United States Food and Drug Administration approved a subcutaneous cardioverter-defibrillator (S-ICD) developed by Boston Scientific as an alternative to transvenous defibrillators (TV-ICD) [2]. In Poland, the first S-ICD devices were implanted in 2014 at the Sterling Memorial Hospital in Łódź as well as at the Department of Cardiology and Electrotherapy of the Medical University of Gdańsk [3]. The aim of this study is to highlight the indications and

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contra-indications to the implantation of the S-ICD, the advantages and limitations of S-ICD and the perspectives for its development to include ventricular pacing and antitachycardia pacing (ATP).

Materials and methods

This is a narrative type of review, no statistical calculations were performed. Independent English and Polish-language literature search has been done by the first author (BON) using the ESC Guidelines, AHA/ACC/HRS Guidelines, the PubMed database and a review article published in "Kardiologia po Dyplomie." We used a query containing the keywords "S-ICD" or "Subcutaneous Cardioverter Defibrillator" and "EV-ICD" and other keywords relevant to the topics of our interest e.g. ventricular pacing, antitachycardia pacing (ATP), new perspectives. Authors focused on articles published in the last 7 years.

Results

The search retrieved 56 records. After review of the abstracts and full texts, 15 articles were included in the analysis.

Discussion

Advantages

The first official recommendations about S-ICD implantations were published in the European Society of Cardiology (ESC) guidelines in 2014 [4]. Therein it was recommended to implant S-ICD in patients with hypertrophic cardiomyopathy who qualify for cardioverter-defibrillator device and at the same time do not have indications for permanent cardiac pacing (class IIb recommendation). In 2015 a class IIa recommendation suggested S-ICD implantation as an alternative to TV-ICD for all patients who do not require permanent cardiac pacing, including cardiac resynchronization therapy (CRT) and antitachycardia pacing (ATP) [5]. An S-ICD device does not have transvenous leads, therefore it is a perfect option for patients who have a difficult vascular access (particularly those with vascular anomalies), venous thrombosis, history of electrotherapy complications (e.g. lead damage, lead extraction) or high risk of endocarditis (e.g. patients treated with immunosuppressants or dialysis). According to the 2017 AHA/ACC/HRS guidelines, S-ICD implantation is a class I recommendation [6].

In addition, S-ICD is also recommended for young patients with heart defects and ventricular arrhythmias. Due to their long expected lifespan, young patients have a high risk of transvenous lead damage or cardiac device-related infective endocarditis (class IIb recommendation) [5]. S-ICD is also a very good solution for patients suffering from cardiac device-related endocarditis (CDE)

S-ICD is implanted at the operating room, usually under general anesthesia though local anesthesia is also an option. The first incision is made between the left mid- and posterior axillary lines in the 5th or 6th intercostal space. The pocket for the S-ICD device is usually made under the latissimus dorsi muscle, however subcutaneous or under the serratus muscle are also acceptable. The device can weighs 130 g and has the volume of 60 cm^3. The defibrillating lead consists of 2 sensing rings and 8 cm-long shock coil. The next step consists of inserting the lead subcutaneously from the device pocket in the direction of the xiphoid process (2nd incision). The distal part of the lead is inserted along the left sternal margin and fixed near the jugular notch (3rd incision). Currently the two-incision technique is preferred, which is safer for patients as it omits the 3rd incision (superior parasternal incision). The three-incision technique may be performed in selected patients with high BMI. During this procedure the patient is exposed to little ionizing radiation, as fluoroscopy is needed only during the initial positioning of the lead and device can. Once the S-ICD is implanted and the patient does not have contraindications, a defibrillation test is performed using a single 65 J impulse. In case of ineffective defibrillation, a second test is automatically attempted using 80 J. In case of second failed defibrillation, it is necessary to revise the device and lead placement. Incorrect placement of the S-ICD device or lead relative to the heart are the most common causes of ineffective defibrillation. This is often due to implating the S-ICD device too superficially [7].

The S-ICD device recognizes arrhythmia via analyzing the electric potentials recorded from the surface of the chest using one of 3 vectors: primary (between the proximal pole of the lead along the sternal margin and the body of the device, secondary (between the distal pole of the lead and the device can and alternate (between the two rings of the lead). Quality of the electric signals obtained from the heart is essential for correct function of the S-ICD the device. Therefore, while qualifying the patient for S-ICD implantation it is necessary to screen the patient for correct arrhythmia recognition. This is done using the manufacturer's programming system to record and analyze the ECG obtained from precordial leads placed similarly to S-ICD leads and device. At least one of the 3 analyzed vectors should be accepted for use in future S-ICD implantation. The vector screening should be performed in several body positions – at minimum while supine and standing upright. During this screening the following parameters are automatically analyzed: voltage, R and T waves (their shape and relation to one another). In case of recognizing a ventricular arrhythmia, the implanted S-ICD device discharges 80 J of energy (up to 5 discharges during a single arrhytmia event) [8].

In January 2022 an analysis of a 5-years long follow-up of 984 patients with S-ICD from the EFFORTLESS register was published. Effectiveness of the high energy defibrillation was confirmed in this heterogenous study group. Relatively few patients required S-ICD removal and replacement with TV-ICD for the purpose of pacing. Episodes of arrhythmias that were either self-limiting or terminated by defibrillation were a predictor of future use of high-energy therapy. Early complications in the 1st year of follow-up were not predictive of late complications. In a 5-year registry the surgical site infections were rarely reported (3.2%), along with erosions (2.3%) and haematomas (0.9%). Lead damage were not observed in this registry [9]. Occasional damage were observed in the third-generation SQ leads. The implantation of a generator pocket between the serratus anterior and the latissimus dorsi muscles improves patients' comfort and reduce site complications. Intermuscular generator pocket and two--incision technique is now the standard of S-ICD implantation.

Limitations

Besides many advantages, an implanted S-ICD device are also has limitations due to the lack of antitachyarhythmic pacing. Another limitation is lack of permanent pacing function. Instead it can only provide pacing for up to 30 seconds, to treat bradyarrhythmia that began directly after defibrillation [5]. Furthermore, the S-ICD's arrhythmia detection based on R and T wave analysis might not be accurate enough for patients with broad QRS complexes in the course of ventricular pacing. Inadequate interventions are another significant problem in the treatment using S-ICD. Initially, 7-13% of interventions were inadequate. Thanks to new arrhythmia recognition algorithms it was possible to reduce inadequate interventions down to 4% during 18 month follow-up since implantation [10]. The most frequent surgical complication of S-ICD implantation are: dislocations of the lead or device can, pressure ulcers in the device pocket and problems with post-operative wound healing. As the operators gained more experience the number of these complications decreased to 3% [5, 11].

New perspectives

Research is underway with the aim of design an optimal implantable subcutaneous device that would combine the functions of a cardioverter-defibrillator and a pacemaker. In some cases, a decision was made to implant an S-ICD device in a patient who already has an implanted pacemaker or vice-versa. In several patients both devices functioned simultaneously without any interference in sensing. Furthermore, no inappropriate defibrillations were noted and none of the devices had to be removed during the 17-month follow-up. However, studies with larger patient groups are needed in order to determine the indications for combining a pacemaker system with an S-ICD device [12].

The previously-mentioned limitation of S-ICD, lack of permanent pacing and ATP might be overcome by an extravascular (EV) ICD by Medtronic that is currently in clinical trials. In this EV-ICD system the defibrillating lead is implanted substernally which allows ATP and bradyarhythmia pacing in addition to the detection and treatment of ventricular fibrillation [13]. In 2019 the first pilot EV-ICD implantations in 20 patients took place at 4 centers in Australia and New Zealand without any significant peri-operative complications. All patients underwent the defibrillation test and in 18 patients (90%) the arhythmia was correctly sensed and sinus rhythm was restored. The average defibrillation threshold was 15 J, whereas pacing energy of < 10V was effective in > 95% of patients. One patient had ventricular tachycardia which was correctly sensed and terminated by ATP. Based on these results, the effectiveness of EV-ICD was comparable to the existing ICD systems [14].

After the promising results of the pilot study, Medtronic began a multi-center, prospective, non-randomized clinical trial that included 400 patients from 60 centers in Asia, Australia, Europe, Middle East, North America and New Zealand. Effectiveness of the defibrillation test is the hard endpoint. Lack of significant general and peri-operative complications suggests this device's safety. The results of this trial are currently analyzed and are likely to be published during this year's EHRA (European Heart Rythm Association) Congress [15].

Conclusions

S-ICD is an effective and safe method of preventing SCD. The main advantages of this device is its implantation outside of blood vessel, high effectiveness and relatively low incidence of early and late post-operative complications. Due to its limitations, S-ICD is currently dedicated for patients without indications for ventricular pacing and ATP. The possibility of combining S-ICD with a pacemamker is currently explored. The main limitations of this approach are the mutual interferences of sensing.

Funding

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Conflicts of interests

None.

References

1. Paratz ED, Rowsell L, Zentner D, Parsons S, Morgan N, Thompson T, et al. Cardiac arrest and sudden cardiac death registries: a systematic review of global coverage. Open Hear [Internet]. 2020 Jan 20;7(1):e001195. Available from: https://openheart.bmj.com/lookup/doi/10.1136/openhrt-2019-001195
2. Chue CD, Kwok CS, Wong CW, Patwala A, Barker D, Zaidi A, et al. Efficacy and safety of the subcutaneous implantable cardioverter defibrillator: a systematic review. Heart [Internet]. 2017 Sep;103(17):1315–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28687562
3. Kaczmarek K, Zwoliński R, Bartczak K, Ptaszyński P, Wranicz JK. A subcutaneous implantable cardioverter-defibrillator – the first implantation in Poland. Kardiol Pol [Internet]. 2015;73(1):62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25625342
4. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J [Internet]. 2014 Oct 14;35(39):2733–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25173338
5. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Rev Esp Cardiol (Engl Ed) [Internet]. 2016 Feb;69(2):176. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26837728
6. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Hea. Hear Rhythm [Internet]. 2018 Oct;15(10):e73–189. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29097319
7. Kaya E, Rassaf T, Wakili R. Subcutaneous ICD: Current standards and future perspective. Int J Cardiol Hear Vasc [Internet]. 2019 Sep;24:100409. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31453314
8. Kempa M. Zastosowanie podskórnego kardiowertera-defibrylatora w prewencji nagłego zgonu sercowego [in Polish]. Kardiol po Dyplomie [Internet]. 2020;(6):36–9. Available from: https://podyplomie.pl/kardiologia/35504,zastosowanie-podskornego-kardiowertera-defibrylatora-w-prewencji-naglego-zgonu-sercowego
9. Lambiase PD, Theuns DA, Murgatroyd F, Barr C, Eckardt L, Neuzil P, et al. Subcutaneous implantable cardioverter-defibrillators: long-term results of the EFFORTLESS study. Eur Heart J [Internet]. 2022 Jun 1;43(21):2037–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35090007
10. Gold MR, Lambiase PD, El-Chami MF, Knops RE, Aasbo JD, Bongiorni MG, et al. Primary Results From the Understanding Outcomes With the S-ICD in Primary Prevention Patients With Low Ejection Fraction (UNTOUCHED) Trial. Circulation [Internet]. 2021 Jan 5;143(1):7–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33073614
11. Boersma L V, El-Chami MF, Bongiorni MG, Burke MC, Knops RE, Aasbo JD, et al. Understanding Outcomes with the EMBLEM S-ICD in Primary Prevention Patients with Low EF Study (UNTOUCHED): Clinical characteristics and perioperative results. Hear Rhythm [Internet]. 2019 Nov;16(11):1636–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31082539
12. Kuschyk J, Stach K, Tülümen E, Rudic B, Liebe V, Schimpf R, et al. Subcutaneous implantable cardioverter-defibrillator: First single-center experience with other cardiac implantable electronic devices. Hear Rhythm [Internet]. 2015 Nov;12(11):2230–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26073595
13. van Dijk VF, Boersma LVA. Non-transvenous ICD therapy: current status and beyond. Herz [Internet]. 2021 Dec;46(6):520--5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34751802
14. Crozier I, Haqqani H, Kotschet E, Shaw D, Prabhu A, Roubos N, et al. First-in-Human Chronic Implant Experience of the Substernal Extravascular Implantable Cardioverter-Defibrillator. JACC Clin Electrophysiol [Internet]. 2020 Nov;6(12):1525--36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33213813
15. Crozier I, O'Donnell D, Boersma L, Murgatroyd F, Manlucu J, Knight BP, et al. The extravascular implantable cardioverter-defibrillator: The pivotal study plan. J Cardiovasc Electrophysiol [Internet]. 2021 Sep;32(9):2371–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34322918

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REVIEW ARTICLE

The role of biomarkers in early prediction and molecular mechanisms of preeclampsia

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Abstract

Preeclampsia (PE) is defined as new onset hypertension after 20 weeks of gestation with evidence of maternal organ or uteroplacental dysfunction or proteinuria. PE is a leading cause of maternal death, with about 55000 deaths worldwide each year. Toxic substances that damage the maternal vascular endothelium induce PE, resulting in liver and kidney malfunction. It is crucial for obstetricians to identify as early as possible the patients who are at risk for PE. Polycystic ovarian disease, sleeping disorders, urinary infections, periodontal disease, smoking, lifestyle and familial history of PE are the major risk factors involved in this disease. VEGF, sFlt1, sENG, PAPP-A, inhibin A and activin A proteins, fetal hemoglobin, heat shock protein and placental protein have been helpful in predicting or diagnosing PE and in understanding its pathogenesis. In addition, a better understanding of PE pathogenesis would aid in identifying the most effective treatments that do not impair the fetus' prognosis. The aim of our study is a review of the pathophysiology and biomarkers, such as pro- and anti-angiogenic substances, that may be useful in the detection of PE in the future.

Keywords: risk factors · biomarkers · angiogenic factors · preeclampsia

Citation

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Introduction

Gestational hypertension is a condition that increases blood pressure by > 140 mmHg in the systolic and > 90 mmHg in the diastolic for the first time 20 weeks into the pregnancy without proteinuria. Preeclampsia (PE) is defined as new onset hypertension after 20 weeks of gestation with evidence of maternal organ or uteroplacental dysfunction or proteinuria. Additionally, both the mother and the child may develop diabetes mellitus or cardiovascular illnesses later in life due to PE. There are two types of PE: early onset (symptoms appearing before 33 weeks) and late-onset (symptoms appear after 34 weeks) [1-2]. Although early and late-onset PE is related to some risk factors and overlaps in presenting symptoms, their effects on both mother and child can differ [3]. Placental perfusion problems cause proteinuria, edema, and multiple organ failure. Clinical signs range from mild to severe hypertension. Preeclampsia symptoms include cephalgia, impaired vision, light sensitivity, weariness, emesis, upper right abdomen pain, dyspnea and contusions. Normal pregnancy alters the patient's immune system, allowing her to withstand illnesses. Because the fetus expresses paternal antigens, a pregnant woman's immune regulatory competence is critical for a safe pregnancy [4]. In PE, genetic and environmental factors contribute to the aetiology and pathophysiology of the disease. The delivery of the fetus and placenta is recognized as the only effective treatment [5].

PE is the leading cause of maternal mortality, accounting for around 55000 fatalities globally each year [6]. It has a complex etiology with early family-based research showing a role for maternal, fetal and paternal genetic factors [7]. We expect the global prevalence of preeclampsia to range from 5% to 14%, with developing countries experiencing a 4% increase. The total prevalence of preeclampsia varies between studies and populations, ranging from 4% to 23% (4% of pregnancies in the United States, 4.74% in Ethiopia, 6.1% in Kenya and 2-14% in Nigeria) [8]. According to the WHO, PE is common in middle-income developing nations such as India, with a 15% incidence rate and more cases in in that country's northern part than in southern. Tripura, the Indian state with the highest PE prevalence, has has demonstrated reduction of risk factors such as smoking and multiple pregnancy terminations. Climate change is also a key risk factor in India, with preeclampsia being more common in the summer and spring. Exposure to sunshine, variations in vitamin D deficiency cigarette consumption, lifestyle and ethnicity are the leading causes of hypertension in India [9-10].

According to the 2019 National Institute for Health and Care Excellence (NICE) guidelines, a pregnant woman with a history of autoimmune disease, diabetes or kidney disease| has an increased risk of PE. Various risk factors, including nulliparity, older age, chronic hypertension and gestational diabetes, have been identified as contributing to the high risk of PE. In addition, women with PE have a higher chance of having cardiovascular, kidney or neurological illness later in life, affecting the child's future health [11-12]. Additional clinical factors that enhance the risk of PE include sleep apnea, polycystic ovarian syndrome and infections (including urinary tract infections, periodontal disease and helicobacter pylori). Changing one's lifestyle can reduce PE, e.g. a vegetable and plant-based diet might be linked to a lower incidence of preeclampsia [13]. The aim of this study was to review the pathophysiology and biomarkers, such as pro- and anti-angiogenic substances.

Material and methods

The electronic databases such as PubMed, EMBASE and Cochrane Library were searched for articles published in the years 2010-present. The search terms were: preeclampsia, biomarkers, pathophysiology of PE, risk factors for PE, genetics of PE. We included only the human studies. Papers not written in English were excluded. This is a narrative review, therefore no statistical analysis was performed.

Results

The search retrieved 85 article abstracts. After screening, 26 of them were excluded and we screened the full texts of the remaining articles. A total of 59 articles were included in the review.

Pathophysiology of PE

The pathogenesis of PE is unknown. Currently PE is commonly thought to be a two-stage disease. The first stage is reduced placental perfusion, caused by abnormal implantation and placental vascular development, due to an imbalance in angiogenic factors [14]. The second stage of PE, maternal response, is manifested by widespread inflammation and maternal endothelian cell dysfunction, increased markers of oxidative stress, insulin resistance, reduced immune function and dyslipidemia [15].

Stage 1

Abnormal placentation

During normal placental development, extravillous cytotrophoblast invades the decidual and myometrial spiral arteries [14]. These spiral arteries then lose their endothelial nature and transform themselves from high resistance

vessels into large vessels capable of providing adequate placental perfucion to supply nourishment to the developing fetus. This results in impaired spiral artery remodelingand relative placental ischemia. A trophoblast defect can cause shallow placentation, placental ischemia, insufficient spiral artery transformation and the maternal syndrome of preeclampsia [16-17]. The inability of preeclamptic trophoblast cells to change epithelial cell surface integrin expression to an endothelial phenotype restricts their ability to penetrate. In addition, PE may disrupt the activity of decidual natural killer (NK) cells, which play a role in vascular remodeling [18-19].

The NK cells produce angiogenesis-promoting cytokines and proteins but cannot remodel spiral arteries downstream. Furthermore, PE has been shown to activate circulating T and NK cells. In addition, PE may also occur due to the lysis of HLA-G deficient trophoblast cells caused by the uterine NK cells. Additionally, the absence of trophoblast cells, which should infiltrate the developing spiral arteries, would prevent the placenta from receiving enough oxygen and nutrients. According to recent research, there may be at least one common cause of spontaneous abortion or infertility. This cause is virtually identical to the cause of PE in pregnancies that survive 20 weeks. A recent study indicates that spiral arteries develop relatively narrow, thick-walled, and tortuous vessels in preeclampsia due to the failure of endovascular trophoblast invasions to undergo physiological modification.

Moreover, in PE, trophoblasts do not invade the myometrial segment of spiral arteries, in contrast to a normal pregnancy, in which the transformation of the spiral artery is limited to the decidual region of one-third of the myometrium. Consequently, deep placentation is unsuccessful and the placenta's blood flow is constrained, resulting in insufficient perfusion by the uterus. This phenomenon is associated with PE as well as many other pregnancy complications, such as placental abruption, preterm labor, premature rupture of membranes and intrauterine fetal mortality [20].

Hypoxia-inducible factors

Hypoxia-inducible factors (HIF) 1α and 2α, markers of cellular oxygen deficiency, were detected in high quantities in the placentas of PE patients. The production of sFLT1 (soluble fms-like tyrosine kinase 1), a solid anti-angiogenic factor associated with the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), is inhibited when 2-methoxyestradiol suppresses HIF-1α, an estradiol metabolite that destabilizes HIF-1α. Because many variables besides hypoxia control HIF-1α expression, identifying the dysregulated signal upstream is difficult [21-22]. During placental hypoxia, the transforming growth factor family three (TGF-3) becomes more active, inhibiting the invasion of trophoblasts and the development of cytotrophoblasts. A natural metabolite of estradiol can decrease placental hypoxia; 2-methoxy estradiol, a natural metabolite of estrogen, reduces placental hypoxia by inhibiting HIF-1α expression. 2-methoxy estradiol is elevated throughout the 3rd trimester of normal pregnancy [23].

Oxidative stress

A pro-oxidant-antioxidant imbalance favours oxidation, which results in oxidative stress (OS). However, uncontrolled lipid peroxidation can occur in PE, impairing normal endothelial cell function [24]. According to research, PE contributes to placental oxidative stress by causing hypoperfusion and ischemia through remodeling of spiral arteries and cytotrophoblast invasion. The placenta experiences oxidative stress during a normal pregnancy due to increased mitochondrial activity, resulting in excess reactive oxygen species (ROS). However, improper placentation amplifies this impact during preeclampsia [23]. Preeclamptic trophoblasts cultured ex vivo produce more ROS, inhibiting the Wnt/-catenin signaling pathway and increasing trophoblast invasion. In addition, anti-angiogenic factors, such as sFLT1, may be expressed [25].

Stage 2

Angiogenic growth factors

Numerous molecules govern the processes of angiogenesis and vascular homeostasis. The VEGF (vascular endothelial growth factor), PlGF (placental growth factor), soluble fms-like tyrosine kinase (sFlt1; fms – feline McDonough sarcoma) and soluble endoglin (sEng) have all been related to the pathophysiology of PE in humans. Endothelial cell activity is required for VEGF, mainly in the liver, glomeruli, and brain, the primary organs affected by preeclampsia. It is a disulfide-linked glycoprotein that is a homodimer involved in angiogenesis and vasculogenesis [26]. The VEGF subfamily functions by interacting with tyrosine kinase receptors, such as EGFR-1, VEGFR-2, and VEGFR-3, that activate cellular responses by phosphorylating the substrate. VEGF and its receptors significantly produced invasive cytotrophoblast in the first trimester of pregnancy for placental vascular development [15]. PlGF is a VEGF family member that plays a role in angiogenesis by binding to VEGFR1/sFLT [27]. It is a powerful angiogenic protein with structural similarity to VEGF that is primarily produced by the placental syncytiotrophoblast. It is also necessary for vasculogenesis during embryonic development in a normal pregnancy. They observed plGF levels to be lower in PE. Women predisposed to PE had lower PlGF levels, whereas salt-1 levels were higher. In PE, sFlt-1 binds to both VEGF and PlGF, inhibiting them from attaching to endogenous receptors. The levels of sFLT1 protein in maternal

plasma or serum were high in preeclamptic placentas [28]. Transforming growth factors (TGF) family members, such as TGF-beta 1 and TGF-beta 3 have a cell surface co-receptor called endoglin. These two substances are powerful inhibitors of trophoblast differentiation and migration. The PlGF, TGF-β and sEng are highly expressed in placental tissue in PE [29].

Angiogenic markers

Soluble Endoglin (sEng)

Cellular endoglin is present on the membranes of vascular endothelium and syncytiotrophoblast cells. It functions as a receptor which inhibits the angiogenic factors TGF-β1 and TGF-β3. Its other function is inhibition of nitric oxide (NO) synthase in the endothelial cells, preventing vasodilatory action via the TGF. Several studies show that endoglin has been linked to PE (Figure 1). According to one study, endoglin mRNA and sEng levels were four times greater in preeclamptic women. According to further research, the level of sEng is also used as a prognostic marker. Concentrations of sEng were three-fold higher in patients with mild PE, five fold in severe PE and ten-fold in those with the HELLP syndrome [30]. During PE, placental endoglin is released into the maternal bloodstream, allowing soluble endoglin to become available. A potential mechanism of action is its ability to interfere with TGF-β1 signaling in the vasculature.

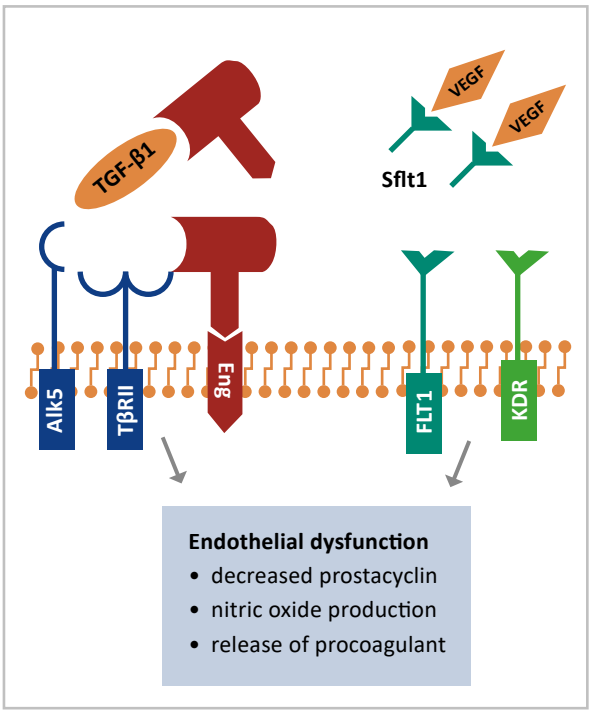

Figure 1. sEng and sFLT-1 cause endothelial dysfunction and leads to preeclampsia

Using adenoviral vectors, over-expression of sEng in rats resulted in improved vascular permeability and mild hypertension without significant proteinuria. Because of over-expressing sFlt1 and sEng with an adenoviral vector, significant vascular damage, nephrotic range proteinuria, severe hypertension, a condition similar to HELLP syndrome, and fetal growth retardation were observed. It is possible, therefore, that sEng and sFlt1 act in different ways to cause endothelial dysfunction and severe PE [31].

Soluble Fms Like Tyrosine kinase-1 (sFLT-1)

The membrane-bound Flt-1 protein (sFlt-1), a shortened splice variant, circulates freely in the bloodstream and binds to PlGF and VEGF. The link between elevated sFlt-1 and PE has been shown in several studies. Levels of sFlt-1 are strongly linked to illness severity, hypertension, and proteinuria [32-33]. In patients with PE, the concentration of sFlt1 rises in the placenta or blood, while PlGF decreases. During the second trimester, sFlt1 and PlGF have shown significant sensitivity in predicting the development of PE (Figure 1) and a high sFlt1:PlGF ratio may also indicate this condition. However, additional clinical research, particularly randomized trials, will be required to determine their utility [34].

Immunological markers

Pregnancy-associated placental protein A (PAPP-A)

The trophoblast produces PAPP-A, a large glycosylated protein thought to function in the implantation process [35]. It enters the maternal bloodstream and binds to the binding protein of eosinophils, inhibiting their proteolytic activity [36]. The first-trimester serum PAPP-A levels are low before other pregnancy problems (e.g. fetal growth restriction, spontaneous miscarriage, placental abruption, premature delivery, gestational diabetes) occur, limiting its use as a PE biomarker (Figure 2). PAPP-A has been proposed as a better diagnostic for fetal growth restriction than preeclampsia [37].

Placental protein 13

Placental Protein 13 (PP13), also known as Galectin 13 (Gal-13) is a polypeptide that combines carbohydrates and is associated with swelling, autoimmune response and cell death. Galectins are vital in controlling certain parts of the genital system in some individuals. It has extreme affinity for sugar residues, namely the ABO blood type antigens AB and B. It may stimulate endometrial arterio-venous dilation and preserve maternal vascular integrity by interacting with glycoproteins and glycolipids [38]. According to studies,

decreased blood PP13 during premature birth may act as a biomarker to identify PE patients. There are some reports that that blood PP13 levels and uterine artery Doppler examination could help to detect individuals with PE before 34 weeks of gestation [39-41]. PE may also be associated with reduced PP13 expression in the placenta [42]. Although PP13 has some predictive significance for PE, Giguere et al needed more data to allow a more precise assessment [43].

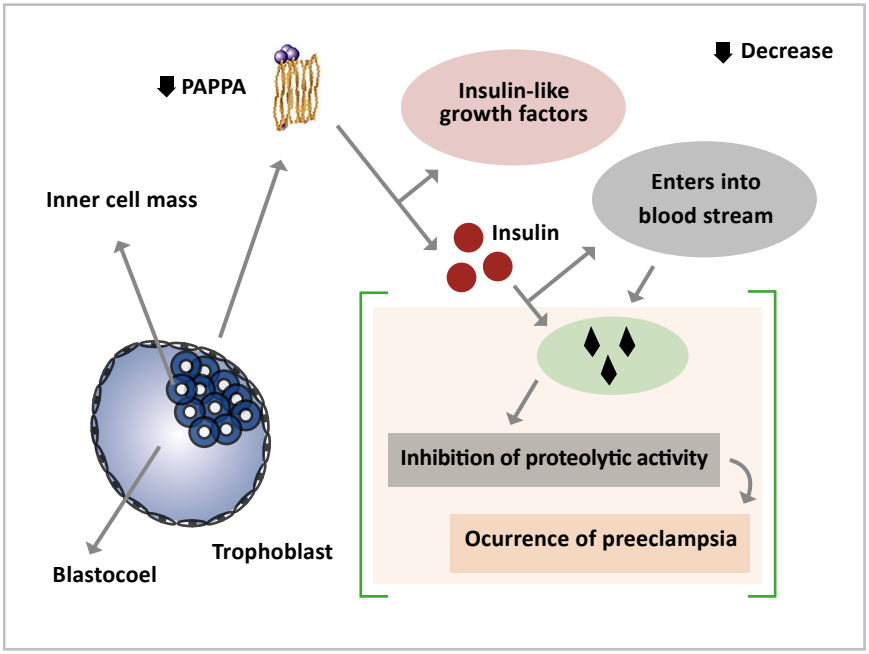

Figure 2. Low levels of the PAPPA protein and the pathogenesis of preeclampsia

Metabolic Marker

Visfatin

It is known that visfatin, a nicotinamide phosphoribosyl transferase enzyme, is produced by adipose tissue that catalyzes the conversion of 5-phosphoribosyl-1-pyrophosphate into nicotinamide mononucleotide [44]. The levels of maternal plasma visfatin were considerably lower in women with PE and it also linked their levels to the severity of the condition [45] (Figure 3). As a result, larger-scale investigations are needed to assess the relevance of visfatin as a possible PE marker.

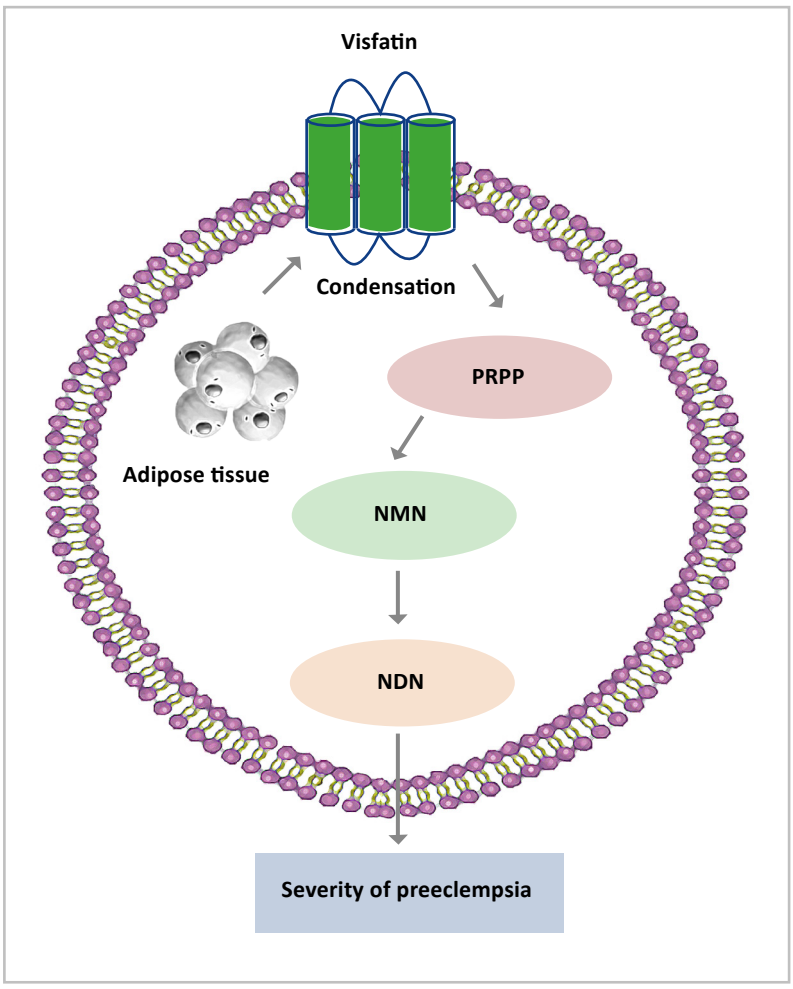

Figure 3. Low-level of visfatin increases the severity of preeclampsia

Endocrine Markers

Inhibin A and activin A

Inhibin A and activin A are glycoprotein hormones that belong to the transforming growth factor-β family. These circulating proteins are primarily obtained from the placenta during pregnancy, and their quantities rise in the third trimester in uncomplicated pregnancies [46]. Inhibin A plays a vital part in the negative feedback of gonadotropins in the endocrine system and Activin A is engaged in various

biological functions. Both hormone concentrations rise in the third trimester of a normal pregnancy and their levels rise tenfold with severe PE. In addition, it causes an increase in maternal oxidative stress and systemic inflammation. Oxidative stress stimulates the production and release of activin A in placental explant and endothelial cells. There are conflicting reports on the increase of inhibin A in the second trimester, which was not as high in PE as Activin A (Figure 4) [47].

Fetal hemoglobin

In PE, fetal hemoglobin (HbF) may provoke oxidative stress. In the placentas and bloodstreams of women with PE, oxidative stress is present. The connection between HbF and PE has prompted researchers to investigate it recently. They have postulated that HbF takes part in PE by causing harm to the placenta, kidneys and other organs, although the actual mechanism remains unknown. Therefore, during PE the placenta has an elevated activity of α1-microglobulin (A1M), showing that oxidative stress responds to its transcription. HbF causes tissue damage that A1M partially alleviates. There may be a possibility of further research on PE using A1M [48]. The fusion of hemoglobin was increased in the placentas of PE patients due to endothelial injury and inflammation [49]. During oxidative stress, patients with PE can have HbF released into their bloodstream. Since the HbF serum of PE patients can be higher during premature gestation, it may be a helpful marker [50].

Heat-shock protein

HSP (highly conserved heat shock protein) is typically found in animal/cellular tissues and regulates the cell cycle, immunity and protein synthesis [51]. Concerning the link between HSP and PE, the study focuses mainly on HSP7070, which may may inhibit apoptosis in various biological processes, including protein function. Maternal adverse reactions, placental disease and oxidative stress can all influence HSP70 expression. A study by Peracoli and colleagues has found that HSP70 may be allied with pro-inflammatory cytokines such as TNF-α, interleukin-1β, and interleukin-12 [52]. Salt-induced hypertension is an outcome of HSP70 overexpression [53]. Livingston et al. demonstrated that the serum HSP70 concentration in women with severe PE is not higher than usual [54--56]. Because of this contradiction, Saghafi et al. performed a meta-analysis and discovered elevated HSP70 serum levels in PE patients compared to women with normal pregnancies [57]. In addition, Hromadnikova et al. found that patients with PE had elevated levels of HSP70 mRNA. It may be possible to examine HSP70 for PE diagnosis, although most data is from case-control studies and prospective studies are rare [58]. The potential biomarkers' functions and their possible use are mentioned in Table 1.

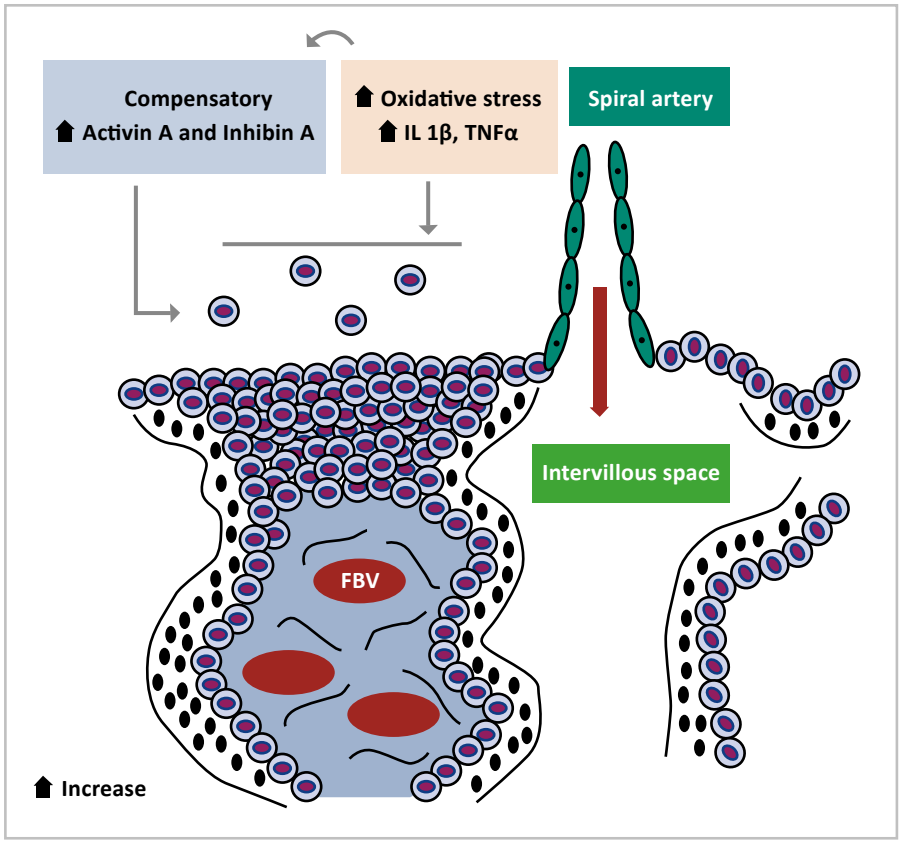

Figure 4. Actin A and Inhibin A are responsible for the manifestation of preeclampsia

Conclusion

Several pregnancy-associated illnesses are associated with PE, which has no known cause. The presence of several protein biomarkers is associated with PE. The following proteins help predict or diagnose PE and aid in the understanding of its pathogenesis: VEGF, sFlt1, sENG, PAPP-A, inhibin A, activin A, fetal hemoglobin, heat shock protein and PP13. Screening for these biomarkers during pregnancy might be clinically helpful. Future research should focus on

Table 1. Biochemical prediction marker for preeclampsia

Biochemical marker	Group	Preeclampsia biomarkers and their potential roles	Potential use
sEng	Angiogenic marker	A protein that inhibits the growth of angiogenic cells	Prognosis/diagnosis
sFlT-1		The placenta is responsible for regulating angiogenesis	Diagnosis
PAPP-A	Immunological marker	A fetus with normal chromosomes probably influences the development of the placenta	Diagnosis
PP-13		A member of the Galectin family, its function remains unknown, but it is believed to induce apoptosis in specific immune cells	Diagnosis
Visfatin	Metabolic marker	It plays a role in glucose homeostasis, and dysregulation of its biosynthesis or signal transduction contributes to disease pathogenesis	Diagnosis
Inhibin A and Activin A	Endocrine marker	It is assumed that inhibition A plays an influential endocrine role in the negative feedback of gonadotrophins. In contrast, activin A is believed to function in various biological tissues	Diagnosis
Fetal Hemoglobin	-	As an antioxidant and heme scavenger, A1M is located in the fetus and is involved in oxygen transport	Diagnosis
Heat shock protein	-	A highly conserved protein that is widely present in organisms and cells and plays a key role in the formation of protein complexes, the regulation of the cell cycle, and the regulation of the immune system	Diagnosis

determining the molecular processes behind the altered angiogenesis and finding new and accurate biomarkers for early disease detection.

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Conflicts of interest

No relevant financial or non-financial conflicts of interests to report.

References

1. Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiolgy. Cardiovasc J Afr [Internet]. 2016 May 18;27(2):71-8. Available from: http://cvja.co.za/onlinejournal/vol27/vol27_issue2/#17/z
2. O'Tierney-Ginn PF, Lash GE. Beyond pregnancy: modulation of trophoblast invasion and its consequences for fetal growth and long-term children's health. J Reprod Immunol [Internet]. 2014;104-105:37-42. Available from: https://www.sciencedirect.com/science/article/pii/S0165037814000540

3. Rizwana A, Rajkumar SA, Anuradha CR. Pregnancy and perinatal outcomes in women with polycystic ovarian syndrome. Int J Reprod Contraception, Obstet Gynecol [Internet]. 2021 Nov 30;10:4232+. Available from: https://link.gale.com/apps/doc/A684661087/AONE?u=anon~90263ab6&sid=bookmark-AONE&xid=6cd48756
4. Varshini GS, Harshini S, Siham MA, Tejaswini GK, Kumar YS, Kulanthaivel L, et al. Investigation of FOXP3 (rs3761548) polymorphism with the risk of preeclampsia and recurrent spontaneous abortion: A systemic review and meta-analysis. Asian Pacific J Reprod [Internet]. 2022;11(3):117. Available from: https://www.apjr.net/article.asp?issn=2305-0500;year=2022;volume=11;issue=3;spage=117;epage=124;aulast=Varshini
5. Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. J Clin Invest [Internet]. 2013 Jul 1;123(7):2775-7. Available from: http://www.jci.org/articles/view/70431
6. Hypertension in Pregnancy. Obstet Gynecol [Internet]. 2013 Nov;122(5):1122-31. Available from: https://journals.lww.com/greenjournal/Fulltext/2013/11000/Hypertension_in_Pregnancy__Executive_Summary.36.aspx
7. Yang Y, Le Ray I, Zhu J, Zhang J, Hua J, Reilly M. Preeclampsia Prevalence, Risk Factors, and Pregnancy Outcomes in Sweden and China. JAMA Netw Open [Internet]. 2021 May 10;4(5):e218401-e218401. Available from: https://doi.org/10.1001/jamanetworkopen.2021.8401
8. Tessema KF, Gebremeskel F, Getahun F, Chufamo N, Misker D. Individual and Obstetric Risk Factors of Preeclampsia among Singleton Pregnancy in Hospitals of Southern Ethiopia. Katsuya T, editor. Int J Hypertens [Internet]. 2021 Jan 20;2021:1-8. Available from: https://doi.org/10.1155/2021/7430827
9. Malik A, Jee B, Gupta SK. Preeclampsia: Disease biology and burden, its management strategies with reference to India. Pregnancy Hypertens [Internet]. 2019;15:23-31. Available from: https://www.sciencedirect.com/science/article/pii/S2210778918301764
10. Agrawal S. Prevalence and Risk Factors for Symptoms Suggestive of Pre-Eclampsia in Indian Women. J Women's Heal Issues Care [Internet]. 2014;03(06). Available from: http://www.scitechnol.com/prevalence-and-risk-factors-for-symptoms-suggestive-of-pre-eclampsia-in-indian-women-tDg6.php?article_id=2389
11. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy. Hypertension [Internet]. 2018 Jul 1;72(1):24-43. Available from: https://doi.org/10.1161/HYPERTENSIONAHA.117.10803
12. Geneen LJ, Webster KE, Reeves T, Eadon H, Maresh M, Fishburn S, et al. Protein-creatinine ratio and albumin-creatinine ratio for the diagnosis of significant proteinuria in pregnant women with hypertension: Systematic review and meta-analysis of diagnostic test accuracy. Pregnancy Hypertens [Internet]. 2021;25:196-203. Available from: https://www.sciencedirect.com/science/article/pii/S221077892100074X
13. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. J Clin Med [Internet]. 2019 Oct 4;8(10):1625. Available from: https://www.mdpi.com/2077-0383/8/10/1625
14. McDonnold M, Olson G. Preeclampsia: Pathophysiology, Management, and Maternal and Fetal Sequelae. Neoreviews [Internet]. 2013 Jan 1;14(1):e4-12. Available from: https://doi.org/10.1542/neo.14-1-e4
15. Silasi M, Cohen B, Karumanchi SA, Rana S. Abnormal Placentation, Angiogenic Factors, and the Pathogenesis of Preeclampsia. Obstet Gynecol Clin North Am [Internet]. 2010 Jun;37(2):239-53. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0889854510000173
16. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? J Clin Invest [Internet]. 1997 May 1;99(9):2152-64. Available from: http://www.jci.org/articles/view/119388
17. Brosens I, Renaer M. ON THE PATHOGENESIS OF PLACENTAL INFARCTS IN PRE-ECLAMPSIA. BJOG An Int J Obstet Gynaecol [Internet]. 1972 Sep 1;79(9):794-9. Available from: https://doi.org/10.1111/j.1471-0528.1972.tb12922.x
18. Lubis MP. Comparison Immunohistochemistry Expression of Desidual Natural Killer (dNK) in Severe Preeclampsia and Normal Pregnancy. Int J Curr Pharm Res [Internet]. 2020;15:58-60. Available from: https://dupakdosen.usu.ac.id/handle/123456789/71546
19. Fukui A, Yokota M, Funamizu A, Nakamua R, Fukuhara R, Yamada K, et al. Changes of NK Cells in Preeclampsia. Am J Reprod Immunol [Internet]. 2012 Apr 1;67(4):278-86. Available from: https://doi.org/10.1111/j.1600-0897.2012.01120.x
20. Hong K, Kim SH, Cha DH, Park HJ. Defective Uteroplacental Vascular Remodeling in Preeclampsia: Key Molecular Factors Leading to Long Term Cardiovascular Disease. Int J Mol Sci [Internet]. 2021 Oct 18;22(20):11202. Available from: https://www.mdpi.com/1422-0067/22/20/11202
21. Rajakumar A, Brandon HM, Daftary A, Ness R, Conrad KP. Evidence for the functional activity of hypoxia-inducible transcription factors overexpressed in preeclamptic placentae. Placenta [Internet]. 2004;25(10):763-9. Available from: https://www.sciencedirect.com/science/article/pii/S0143400404000797

22. Redman CWG, Sargent IL. Placental Stress and Pre-eclampsia: A Revised View. Placenta [Internet]. 2009;30:38-42. Available from: https://www.sciencedirect.com/science/article/pii/S0143400408003950
23. Nirupama R, Divyashree S, Janhavi P, Muthukumar SP, Ravindra P V. Preeclampsia: Pathophysiology and management. J Gynecol Obstet Hum Reprod [Internet]. 2021;50(2):101975. Available from: https://www.sciencedirect.com/science/article/pii/S2468784720303457
24. Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive Cytotrophoblasts Manifest Evidence of Oxidative Stress in Preeclampsia. Am J Pathol [Internet]. 2000;156(1):321-31. Available from: https://www.sciencedirect.com/science/article/pii/S0002944010647335
25. Huang QT, Wang SS, Zhang M, Huang LP, Tian JW, Yu YH, et al. Advanced oxidation protein products enhances soluble Fms--like tyrosine kinase 1 expression in trophoblasts: A possible link between oxidative stress and preeclampsia. Placenta [Internet]. 2013;34(10):949-52. Available from: https://www.sciencedirect.com/science/article/pii/S0143400413005845
26. Esser S, Wolburg K, Wolburg H, Breier G, Kurzchalia T, Risau W. Vascular Endothelial Growth Factor Induces Endothelial Fenestrations In Vitro. J Cell Biol [Internet]. 1998 Feb 23;140(4):947-59. Available from: https://doi.org/10.1083/jcb.140.4.947
27. De Falco S. The discovery of placenta growth factor and its biological activity. Exp Mol Med [Internet]. 2012;44(1):1-9. Available from: https://doi.org/10.3858/emm.2012.44.1.025
28. Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest [Internet]. 2003 Mar 1;111(5):649-58. Available from: http://www.jci.org/articles/view/17189
29. Jones RL, Stoikos C, Findlay JK, Salamonsen LA. TGF-β superfamily expression and actions in the endometrium and placenta. Reproduction [Internet]. 2006;132(2):217-32. Available from: https://rep.bioscientifica.com/view/journals/rep/132/2/1320217.xml
30. Staff AC. Circulating predictive biomarkers in preeclampsia. Pregnancy Hypertens An Int J Women's Cardiovasc Heal [Internet]. 2011;1(1):28-42. Available from: https://www.sciencedirect.com/science/article/pii/S2210778910000139
31. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble Endoglin and Other Circulating Antiangiogenic Factors in Preeclampsia. N Engl J Med [Internet]. 2006 Sep 7;355(10):992-1005. Available from: https://doi.org/10.1056/NEJMoa055352
32. Rajakumar A, Michael HM, Rajakumar PA, Shibata E, Hubel CA, Karumanchi SA, et al. Extra-placental Expression of Vascular Endothelial Growth Factor Receptor-1, (Flt-1) and Soluble Flt-1 (sFlt-1), by Peripheral Blood Mononuclear Cells (PBMCs) in Normotensive and Preeclamptic Pregnant Women. Placenta [Internet]. 2005;26(7):563-73. Available from: https://www.sciencedirect.com/science/article/pii/S0143400404002371
33. Karumanchi SA, Lindheimer MD. Preeclampsia Pathogenesis. Hypertension [Internet]. 2008 Apr 1;51(4):991-2. Available from: https://doi.org/10.1161/HYPERTENSIONAHA.107.100735
34. Gbadegesin A, Agbara JO, Rabiu KA, Sobande AA, Azeez MA. Placenta Growth Factor and Soluble Fms-Like Tyrosine Kinase 1 in Preeclampsia and Normotensive Pregnant Nigerian Women. Open J Obstet Gynecol [Internet]. 2021;11(06):753-62. Available from: https://www.scirp.org/journal/doi.aspx?doi=10.4236/ojog.2021.116070
35. Karumanchi SA. Chapter Fourteen - Biomarkers in Preeclampsia. In: Edelstein CLBT-B of KD (Second E, editor. Academic Press; 2017. p. 555-94. Available from: https://www.sciencedirect.com/science/article/pii/B9780128030141000145
36. Spencer CA, Allen VM, Flowerdew G, Dooley K, Dodds L. Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes. Prenat Diagn [Internet]. 2008 Nov 1;28(11):1029–36. Available from: https://doi.org/10.1002/pd.2116
37. Preiss J, Handler P. Enzymatic synthesis of nicotinamide mononucleotide. J Biol Chem [Internet]. 1957;225(2):759-70. Available from: https://www.researchgate.net/profile/Jack-Preiss/publication/10150760_Enzymatic_synthesis_of_nicotinamide_mononucleotide/links/0deec517ad1fc60e06000000/Enzymatic-synthesis-of-nicotinamide-mononucleotide.pdf
38. Sammar M, Drobnjak T, Mandala M, Gizurarson S, Huppertz B, Meiri H. Galectin 13 (PP13) Facilitates Remodeling and Structural Stabilization of Maternal Vessels during Pregnancy. Int J Mol Sci [Internet]. 2019 Jun 29;20(13):3192. Available from: https://www.mdpi.com/1422-0067/20/13/3192
39. Huppertz B, Meiri H, Gizurarson S, Osol G, Sammar M. Placental protein 13 (PP13): a new biological target shifting individualized risk assessment to personalized drug design combating pre-eclampsia. Hum Reprod Update [Internet]. 2013 Jul 1;19(4):391-405. Available from: https://doi.org/10.1093/humupd/dmt003
40. Nicolaides KH, Bindra R, Turan OM, Chefetz I, Sammar M, Meiri H, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound. Ultrasound Obstet Gynecol [Internet]. 2006 Jan 22;27(1):13-7. Available from: https://doi.org/10.1002/uog.2686

41. Khalil A, Cowans NJ, Spencer K, Goichman S, Meiri H, Harrington K. First trimester markers for the prediction of pre-eclampsia in women with a priori high risk. Ultrasound Obstet Gynecol [Internet]. 2010 Jun 1;35(6):n/a-n/a. Available from: https://doi.org/10.1002/uog.7559
42. Than NG, Balogh A, Romero R, Kárpáti A, Erez O, Szilágyi A, et al. Placental Protein 13 (PP13) â€“ A Placental Immunoregulatory Galectin Protecting Pregnancy. Front Immunol [Internet]. 2014 Aug 20;5:348. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2014.00348/abstract
43. Giguère Y, Charland M, Bujold E, Bernard N, Grenier S, Rousseau F, et al. Combining Biochemical and Ultrasonographic Markers in Predicting Preeclampsia: A Systematic Review. Clin Chem [Internet]. 2010 Mar 1;56(3):361-75. Available from: https://doi.org/10.1373/clinchem.2009.134080
44. Fasshauer M, Blüher M, Stumvoll M, Tönessen P, Faber R, Stepan H. Differential regulation of visfatin and adiponectin in pregnancies with normal and abnormal placental function. Clin Endocrinol (Oxf) [Internet]. 2007 Mar 1;66(3):434-9. Available from: https://doi.org/10.1111/j.1365-2265.2007.02751.x
45. Hu W, Wang Z, Wang H, Huang H, Dong M. Serum visfatin levels in late pregnancy and pre-eclampsia. Acta Obstet Gynecol Scand [Internet]. 2008 Jan 1;87(4):413-8. Available from: https://www.tandfonline.com/doi/abs/10.1080/00016340801976012
46. Kar M. Role of biomarkers in early detection of preeclampsia. J Clin Diagn Res [Internet]. 2014 Apr;8(4):BE01-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24959436
47. Abbas RA, Ghulmiyyah L, Hobeika E, Usta IM, Mirza F, Nassar AH. Preeclampsia: A Review of Early Predictors. Matern Med [Internet]. 2021 Jul 1;3(3):197-202. Available from: https://doi.org/10.1097/FM9.0000000000000088
48. Hansson SR, Nääv Å, Erlandsson L. Oxidative stress in preeclampsia and the role of free fetal hemoglobin. Front Physiol [Internet]. 2015 Jan 13;5. Available from: http://journal.frontiersin.org/article/10.3389/fphys.2014.00516/abstract
49. Centlow M, Carninci P, Nemeth K, Mezey E, Brownstein M, Hansson SR. Placental expression profiling in preeclampsia: local overproduction of hemoglobin may drive pathological changes. Fertil Steril [Internet]. 2008 Nov;90(5):1834-43. Available from: https://www.sciencedirect.com/science/article/pii/S0015028207036539
50. Henry A, Arnott C, Makris A, Davis G, Hennessy A, Beech A, et al. Blood pressure postpartum (BP2) RCT protocol: Follow-up and lifestyle behaviour change strategies in the first 12 months after hypertensive pregnancy. Pregnancy Hypertens [Internet]. 2020 Oct;22:1-6. Available from: https://www.sciencedirect.com/science/article/pii/S2210778920300908
51. Lindquist S, Craig EA. The heat-shock proteins. Annu Rev Genet [Internet]. 1988;22(1):631-77. Available from: https://scholar.archive.org/work/7msluk3e7jel7bb33rnaz57cfe/access/wayback/http://lindquistlab.wi.mit.edu/PDFs/LindquistCraig1988ARG.pdf
52. Peraçoli JC, Bannwart-Castro CF, Romao M, Weel IC, Ribeiro VR, Borges VTM, et al. High levels of heat shock protein 70 are associated with pro-inflammatory cytokines and may differentiate early- from late-onset preeclampsia. J Reprod Immunol [Internet]. 2013;100(2):129-34. Available from: https://www.sciencedirect.com/science/article/pii/S0165037813001034
53. Rodríguez-Iturbe B, Pons H, Quiroz Y, Lanaspa MA, Johnson RJ. Autoimmunity in the pathogenesis of hypertension. Nat Rev Nephrol [Internet]. 2014 Jan 19;10(1):56-62. Available from: https://doi.org/10.1038/nrneph.2013.248
54. Molvarec A, Rigó J, Lázár L, Balogh K, Makó V, Cervenak L, et al. Increased serum heat-shock protein 70 levels reflect systemic inflammation, oxidative stress and hepatocellular injury in preeclampsia. Cell Stress Chaperones [Internet]. 2009 Mar 7;14(2):151. Available from: https://doi.org/10.1007/s12192-008-0067-8
55. Molvarec A, Prohászka Z, Nagy B, Szalay J, Füst G, Karádi I, et al. Association of elevated serum heat-shock protein 70 concentration with transient hypertension of pregnancy, preeclampsia and superimposed preeclampsia: a case–control study. J Hum Hypertens [Internet]. 2006 Oct 1;20(10):780-6. Available from: https://doi.org/10.1038/sj.jhh.1002060
56. Livingston JC, Ahokas R, Haddad B, Sibai BM, Awaads R. Heat shock protein 70 is not increased in women with severe preeclampsia. Hypertens Pregnancy [Internet]. 2002 Jan 1;21(2):123-6. Available from: https://doi.org/10.1081/PRG-120004767
57. Saghafi N, Pourali L, Ghavami Ghanbarabadi V, Mirzamarjani F, Mirteimouri M. Serum heat shock protein 70 in preeclampsia and normal pregnancy: A systematic review and meta-analysis. Int J Reprod Biomed [Internet]. 2018 Jan;16(1):1-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29707695
58. Hromadnikova I, Dvorakova L, Kotlabova K, Kestlerova A, Hympanova L, Novotna V, et al. Circulating heat shock protein mRNA profile in gestational hypertension, pre-eclampsia & foetal growth restriction. Indian J Med Res [Internet]. 2016 Aug;144(2):229-37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27934802

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REVIEW ARTICLE

Presurgical techniques for the treatment of cleft lip and palate in infants – a review of the literature

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Abstract

Patients with cleft lip and palate require long-term, multistage and multidisciplinary treatment whose first step is presurgical orthopaedic (PSO) treatment. The reconstruction of the lip, alveolar process and nose in these patients are major plastic surgery challenges. Various presurgical procedures are undertaken to achieve optimal surgical outcomes. The aim of this article is to present selected techniques for the presurgical cleft lip and palate treatment in infants and critically evaluate the benefits, limitations and drawbacks of the methods used. The research was based on the literature review using keywords: presurgical treatment of cleft lip and palate in infants, presurgical orthopaedics in the treatment of cleft lip and palate in infants in PubMed, Google Scholar databases, and publications in orthodontics and infant orthopaedics out of these databases. PSO is a minimally invasive therapy performed between birth and first surgery. Anatomical and functional cleft palate disorders constitute indications for PSO. There are positive reports on PSO techniques and some of them can be implemented by the child's caregivers at home. The authors of studies disagree on the PSO effectiveness. The lack of long-term research results, high costs of therapy and few therapy centres negatively influence the decision to undertake the therapy.

Keywords: nasoalveolar molding · infant · cleft lip · cleft palate · presurgical orthopaedics

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Introduction

Cleft lip and palate is one of the most common developmental defects, which manifests as an anatomical discontinuity and underdevelopment of the tissues involved in this disorder. Due to abnormalities in the morphology of the skeleton and dentition it causes numerous functional problems (e.g. with breathing, sucking, swallowing, chewing, and speech) and promotes infections of the respiratory tract and middle ear [1]. Often the cleft is also the cause of varying degrees of self-esteem issues and social exclusion. The loss of anatomical continuity of the tissues due to cleft implies a disruption of the harmonious pre- and postnatal growth of all the anatomical structures that are interconnected and control further growth, resulting in deformities of the facial elements, jaws and nose.

The incidence of clefts varies. They are most common in Asians (Indians 3.6/1000, Japanese 2.1/1000, Chinese 1.7/1000) and are less common in African-Americans (0.3/1000). Among Caucasians, the average incidence is about 1/1000, with a fairly high incidence in Europe (Sweden 2/1000 and Denmark 1.9/1000) [2-4].

Cleft lip and palate causes numerous morphological abnormalities in the craniofacial region. Deformities observed in unilateral cleft lip and palate are a more or less pronounced cupid's bow, a poorly marked or absent philtral ridge, shortening of the lip on the cleft side compared to its height on the unaffected side, an often-hypertrophied lip frenulum, the depth of the nasolabial fold usually only marked on the non-cleft side, a protrusion of the cutaneous part of the lip due to the retraction of the underlying muscles which have lost their grip. The nasal deformities associated with this cleft are flattening and widening of the nostril opening on the cleft side, tilt of the columella toward the affected side, upturned base of the nasal wing, deviation of the anterior nasal spike toward the normal side, and asymmetry of the nasal tip. In bilateral cleft lip and palate, the cupid's bow is generally absent and the cutaneous portion of the lip is a convex lens-shaped surface. There is no visible philtral ridge and the prolabium is usually devoid of properly developed muscle fibres. Visible nasal deformities include a flattened and dilated nasal tip, shortened columella, and poorly developed septal nasal cartilage. The premaxilla is protruded, while the cleft jaw fragments collapse towards the midline [5] (Fig. 1).

The treatment of cleft lip and palate in infants requires a multistage, multidisciplinary approach and cooperation between physicians of many specialties. Presurgical orthopaedic (PSO) treatment is one of the earliest stages of this treatment plan. Whereas presurgical orthodontic techniques are used to model the tissues of the jaw, alveolar process, and nose of an infant with unilateral or bilateral cleft lip and palate. According to many authors, infants who have a complete osseous cleft may benefit from PSO treatment applied prior to cleft lip and palate suturing procedures. The expected outcome of PSO treatment techniques is primarily an attempt to achieve better surgical outcomes by reducing the cleft gap and improving jaw growth, making the tissues of the lip and nasal region more flexible [6-7].

Other expected effects of PSO techniques mentioned in the literature are improvement of jaw growth, facilitation of intraoral feeding, improvement of speech function, and reduction of nasal deformity [6-7].

The literature suggests that the use of PSO by the orthodontist early in the child's development, due to the high flexibility of the soft tissues, may offer the possibility of a better surgical treatment outcome. On the other hand, PSO techniques often raise several doubts and there is much discussion in the literature. The aim of this article was to review the literature about selected presurgical treatment techniques for cleft lip and palate in infants and to critically evaluate the their benefits, limitations and drawbacks.

Materials and methods

The literature from 1987-2021 was reviewed using the key words: presurgical treatment of cleft lip and palate in infants, presurgical orthopaedics in the treatment of cleft lip and palate in infants in the PubMed and Google Scholar databases and publications in the field of orthodontics and infant orthopaedics that were not available in the mentioned databases. Based on the analysis of 75 publications, 35 articles, and 2 textbooks related to the topic of the study were selected. Case reports and literature of Polish authors were included in the literature.

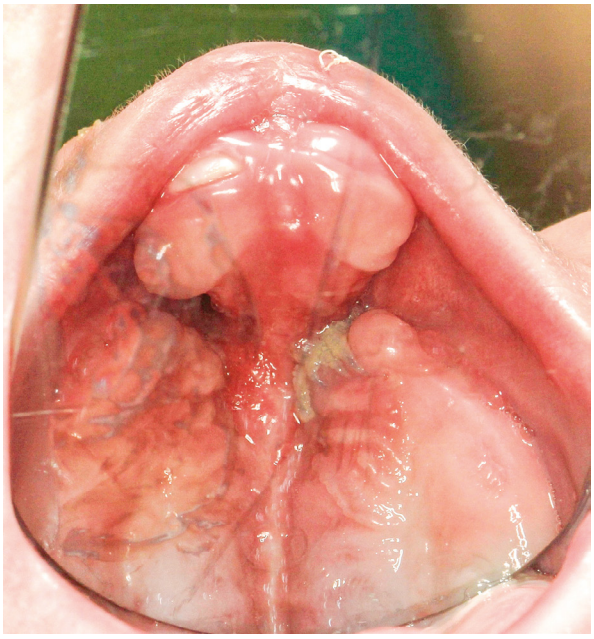

Figure 1. Bilateral cleft palate in an infant

Results

PSO (Presurgical Orthopaedic) treatment is a clinical technique which has its beginning in the seventeenth century, when Hoffman used a headgear with straps which caused the retraction of the premaxilla and narrowing of the cleft fissure. Desault wanted to achieve the same effect with a similar technique in children with bilateral clefts. Later, Hullihen (1844) used adhesive tapes in the presurgical phase to help bring the cleft soft tissues together and Brophy (1927) used a silver wire passing through both cleft segments of the alveolar process, tightening the wire led to approximation of the segments [8]. A little later, McNeil (1950) used acrylic plates to form the cleft segments of the alveolar process [8-9]. Among the methods introduced for the presurgical treatment of clefts we should also mention the acrylic plates immobilised with pins aimed at simultaneous retraction of the premaxilla and expansion of the posterior cleft segments, used by Georgiade and Latham (1975) and the passive acrylic plates used by Hotz (1987). A method combining correction of cleft palate, alveolar process, lip, and nose was proposed in 1993 by B.H. Grayson and was based on the use of an acrylic plate fitted with a nasal stent and tapes [9-11]. Effective treatment of cleft lip and palate should lead primarily to restoration of the continuity of the alveolar ridge, normal oral function, development of the speech apparatus, and improvement of hearing and aesthetics. PSO techniques in their assumption aim to prepare the patient for surgical treatment. The authors of these publications suggest that combining PSO with surgery may contribute to favourable treatment outcomes, increasing the likelihood of improving the quality of life [7, 12].

The application of the chosen PSO therapy depends on the type of cleft and the preference of the treating physician. In the literature the most frequently mentioned PSO techniques are alveolar modelling with palatal plates, tape therapy, massage, and NAM [7].

Alveolar modelling with a palatal plate

Alveolar modelling with a palatal plate takes advantage of the increased formability of the maxillary segments in infants and the possibility of their repositioning. The aim of this treatment is to achieve an end-to-end alveolar position prior to surgical treatment. Active and passive, intraoral or extraoral appliances are used in the treatment. Active plates move the alveolar segments in a specific way with controlled forces, whereas passive appliances do not provide force but act as a support point for the forces generated during surgical suturing of the lip to contour and form the alveolar segments [13-14].

The plates used in PSO have two handles (wires) fused into the anterior part, lying on the cheeks. The plate located in the oral cavity covers the palate and alveolar ridge and covers the cleft fissure, separating the nasal and oral cavities (Fig. 2-3). In patients not treated with a plate, the tongue is located in the cleft fissure, impairs the growth of the jaw and reduces the size of the cleft fissure [15]. Depending on the type of cleft, the plate is relieved accordingly resulting in displacement of the cleft segments [16]. Numerous modifications of the palatal plate are described in the literature, e.g.: Perczyńska-Partyka (with a hole for a dummy), Burston (with a bite shaft), Perzynowa (with an orthodontic screw), Penkalowa (concerning bilateral clefts, with the use of an acrylic pad on the premaxilla) [16]. The following advantages of alveolar modelling with a palatal plate were reported in the literature:

- reduction of cleft fissure size due to growth of alveolar ridges and bones medially [7, 15],

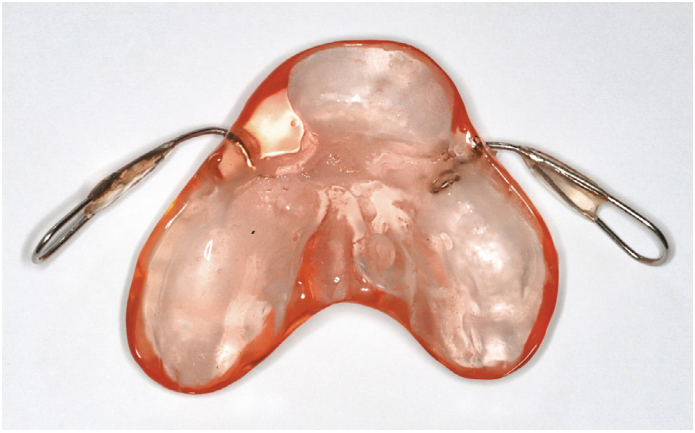

Figure 2. Palate plate made of acrylic. View from the inside

Figure 3. Palate plate made of acrylic. Front view

- improved sucking and swallowing function and the possibility of replacing probe feeding in favour of breastfeeding [7, 16].

Whereas the following disadvantage of this technique was also noted: the headpiece or cloth straps (needed to keep the plate in the correct position) may cause discomfort for the patient [16].

Orthopaedic taping

Orthopaedic taping is commonly used in the presurgical management of cleft treatment. It can both complement another technique or be used as a separate therapeutic tool. External taping is used in conjunction with intraoral plates and is a source of external forces used in the process of alveolar ridge repositioning. The aim of orthopaedic taping is to approximate the soft tissues located in the immediate area of the cleft. The tapes mimic the flexibility and functionality of the muscles. In bilateral clefts, the tapes are placed on the patient's cheeks and apply pressure on the protruding premaxilla to retract it. The forces acting on the cleft segments improve their position. In the case of unilateral clefts, lip protectors attached to the tape are used to facilitate the repositioning of the segments into the correct position. The desired effect of using this method is to change the shape of the lip edges and improve the muscular strength of this area [7, 17-18]. Among the advantages of orthopaedic taping technique is beneficial effect on muscle development, muscle mass gain and enhancement of the child's facial expression [7, 18]. The following disadvantages of this technique are reported in the literature:

- frequent complications: skin irritations, ulcerations [8-9],
- difficulties in maintaining hygiene of the treated area [8, 19],
- mistakes in tape replication by the caregiver [19].

Massage

A PSO technique rarely described in the orthodontic and dental literature is cleft lip massage. The recommended PSO treatment for children with cleft is to massage both parts of the cleft lip. It is recommended that the massage be performed by the child's caregiver several times a day. The massage should be performed in accordance with the recommendations of the orthodontist. Massages are intended to stretch and make soft tissues more flexible before surgery. Szeląg et al. describe the method of massage which depends on the type of cleft [16]. It is recommended to perform massages 3-5 times a day with 30 movements bringing the cleft lips together during one massage [16]. The main advantage of massage is increasing tissue elasticity and stretching, which facilitates surgical procedures (fusion of the cleft parts and formation of the lip) [15]. It should be noted that this is the least invasive of the techniques described [16].

Nasoalveolar Molding (NAM)

The NAM technique is a method particularly popular in the United States and is also used in many European and Asian countries. The aim of the technique is to reduce the oro-nasal deformity prior to primary surgery. The NAM technique uses a palatal plate and wire elements, as well as extraoral nasal stents, supported by surgical tapes. The elements used can lead to narrowing of the cleft fissure, formation of the nasal cartilage, the premaxilla, and the alveolar process. The desired outcome of treatment is to achieve the correct position of the replaced structures and a shape suitable for the neonatal-infant period [9]. According to the authors Grayson et al. [9] in infants with bilateral cleft lip and palate with alveolar involvement, the goals of presurgical NAM are non-surgical elongation of the columella, positioning of the premaxilla in the sagittal plane, and retraction of the premaxilla in a slow and gentle process to achieve continuity with the posterior segments of the alveolar cleft [9]. Additional objectives include reducing the width of the nasal tip, improving its projection, and reducing the width of the nasal wing base [9, 20].

The basis for the NAM concept was a study by Matuso et al. (1984), according to which hormones in infants (higher levels of oestrogen) have a significant effect on the ability to form cartilage tissue [8-10, 13]. The palatal plate is formed depending on the type of cleft, considering the areas of potential pressure and relief. Additionally, it is provided with a retention arm[s] usually ending in a retention button, which allows the attachment of flexible elements: orthodontic extractors, orthodontic elastics and surgical tapes stretched between the retention button and soft tissues of the cheeks. At a later stage of treatment (cleft fissure reduced to 5-6 mm), a stent is added to the plate, which should be beneficial in improving nasal symmetry and protrusion [8].

The NAM technique has many modifications regarding the construction of the palatal plate, the stent, and the treatment procedure. These include, for example, the PENAM technique described by Qi Wang et al. [21] using a nasal frame and stent, without the use of a palatal modelling plate, and the Figueroa NAM technique described by Y-F Chen and Y-F Liao [22] using a passive modelling plate [21-22].

Advantages of the NAM technique reported in the literature are:

- approximation of the cleft segments, alignment of the soft tissues, improved symmetry of the nasal cartilage which allows for better postoperative results with less risk of scarring [8-9, 23],
- a more favourable position of the alveolar process allows bone formation, which in the further development of the child gives a chance for teeth to erupt in the correct positions and the possibility of better alignment of the dentition and periodontal support [8, 24],

- the potential stimulation of immature nasal chondroblasts and their interstitial expansion, resulting in improved nasal morphology [8, 13].

Disadvantages of the technique reported in the literature:

- irritation and ulceration of the oral mucosa, gums, nose, and cheek skin, due to excessive pressure of the plate in the oral vestibular area and on the labial side of the premaxilla, Inflammation of the nasal tip area due to excessive force applied to the nasal stent and fungal infections resulting from poor tissue hygiene [8-9, 13, 25],
- he need for precise fabrication of the plate and its adjustment each time during the follow-up visit [8].

Discussion

A study on the effectiveness of the PSO techniques using a palatal plate was conducted by Mishima et al. [26]. The study involved 20 children (up to 18 months of age) with unilateral complete cleft lip and palate. Twelve children were treated with PSO using a palatal plate. The following parameters were assessed: degree of palatal dislocation, size of segment migration and shape of the alveolar process arch. Compared to the control group, an increase in the size of the palate with a decrease in the gap between the maxillary segments (sagittal axis), a reduction in the angle of the segments towards the nasal cavity and an increase in the migration of the smaller segment towards the larger segment were obtained. According to the authors Mishima et al. [26], the use of braces in PSO can stimulate segment growth and prevent the jaw arch from collapsing under the force of lip closure [26].

A study on the effectiveness of using PSO techniques with the NAM technique was described by Padovano et al. [27], who reviewed 12 studies on the long-term effects of using this technique in patients with unilateral cleft lip and palate. According to the analysis of the data, the use of the NAM technique was found to be beneficial in improving the aesthetic aspect compared to no presurgical treatment with braces [27]. According to Maull et al. [28], the NAM technique has a beneficial effect on nasal shape in patients with unilateral complete cleft. The use of this technique up to 4 months of age followed by primary surgery resulted in better nasal symmetry compared to the control group. The treatment effect persisted into early childhood [28]. Lee et al. [29] compared the results of patients with bilateral cleft treated with surgery with patients treated according to the NAM protocol. They found that non-surgical columella lengthening (NAM) followed by primary retrograde nasal reconstruction had a beneficial effect on columella length and significantly reduced the need for repeat nasal surgery [29].

Based on a long-term evaluation, Lee et al. [30] analysed the effects of alveolar modelling and gingivoperiosteoplasty (modified Millard type) on the growth of the midface in the prepubertal period. They found that presurgical nasoalveolar molding (NAM) and gingivoperiosteoplasty (Millard type) did not affect the growth of the midface in the sagittal or vertical planes (until the age of 9-13 years) [30]. Ringdahl [31], who compared the long-term effects of treatment using the NAM technique with patients in the control group, found no significant difference in midface growth [31].

It should be noted that in numerous articles the authors point out that the use of the NAM technique is associated with the risk of an abnormal process of movement of the larger segment without changing or with a weaker change in the position of the smaller segment, so that the smaller segment becomes blocked. Furthermore, excessive nostril dilatation, resulting from too early placement of the nasal stent, is noticeable [20, 29]. There are also opinions that, despite the beneficial effect on approximation of cleft maxillary segments in the NAM technique or other PSO methods, there are no clear long-term results indicating the benefits of the therapies [7].

Studies on the effectiveness of PSO techniques using kinesiotaping were described by Dajewee et al. [19]. The application of tapes transverse to the cleft fissure with their replacement every 1-3 days depending on the clinical condition of the patient (25% tape tension), applied until the child was 6 weeks old, led to a reduction in the cleft angle (on average from 57.53˚ to 31.3˚) and narrowing of its subnasal width (on average from 36.41 mm to 21.69 mm) as well as approximation of the tissues within the vermillion border (on average from 47.84 mm to 25.48) [19].

Table 1 summarizes the results of studies on the effect of presurgical therapy (see Table 1).

The effectiveness of using PSO techniques is controversial. The literature suggests that there is limited evidence on the long-term effects of the techniques discussed, which may be due to, for instance, the experience of the orthodontist [30]. Authors of publications also point out the need for detailed long-term studies on the efficacy of PSO, as they are mostly conducted with a small study group of a few to a dozen infants [26, 29-30, 32-33]. Certainly, treatment with PSO is a complex and costly therapy, with its effectiveness not unequivocally confirmed. There are few centres applying PSO, which often forces long travelling and generates high treatment costs [6]. According to Ross, a marked visual improvement in the faces of infants treated with PSO compared to those not treated becomes imperceptible over time [34]. Adali et al. found that the use of PSO techniques does not significantly affect the shape of the dental arch in the treatment of children with clefts [35]. Significant changes in its shape were only noticed after surgery [35]. Another argument against PSO is its negative impact on speech development due to delayed surgical closure of the hard palate [7, 36].

Table 1. Summary table of the described methods and effects of presurgical therapies

Author and year	Study group size	Treatment method	Treatment effects
Mishima et al. 1996	20	Palate plate	- large size of palate - smaller sagittal gap between the two segments of the maxilla - smaller steepness of the segments toward the nasal cavity - larger magnitude of migration of the lesser segment toward the cleft edge of the major segment
Maull et al. 1999	20	NAM technique	- increases nasal symmetry to early childhood
Lee et al. 2004	20	NAM technique	- no effects on midface growth in sagittal or vertical planes
Lee et al. 2008	26	NAM technique	- non-surgical lengthening of collumela - reduced the need for secondary nasal surgery
Ringdahl 2011	16	NAM technique	- no significant difference between the molding and non-molding groups in Goslon score, nasal form, nose symmetry, vermilion border or nasolabial profile assessments
Dawjee et al. 2014	8	Lip taping	- reduction in cleft size ranging from 9.1 mm to 36.7 mm
Padovano et al. 2021 (meta-analysis)	12 (studies)	NAM technique – passive presurgical infant orthopedic appliances	- better frontal nasal form and vermillion border

Presurgical techniques for the treatment of cleft lip and palate have been used for more than 60 years. The aim of PSO is to shape the segments of the cleft jaw and stimulate their growth and development. PSO is a preparation for further surgical treatment. Among the indications for PSO are anatomical abnormalities including cleft fissure size and various functional disorders [16]. It is important to note that the authors of the publications are divided and that there are different attitudes regarding the effectiveness of PSO. Published studies prove the effectiveness of PSO and the validity of the use of these techniques as well as those that undermine them.

Conclusion

Based on the analysis of the literature, we concluded that in favour of the use of PSO are multidisciplinary care of the child with a cleft and starting treatment from the first days of life, before surgery, its relatively low invasiveness, the possibility of performing it by the patient's caregivers (e.g., massages, kinesiotaping) and the reports on the potential effectiveness of PSO therapies. Whereas against the use of PSO techniques are contradictory reports of outcomes, lack of long-term evaluation of their effectiveness, limited availability and high cost of treatment.

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Conflicts of interests

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References

1. Ilczuk-Rypuła D, Pietraszewska D, Kempa M, Zalewska-Ziob M, Wiczkowski A. Methods of cleft lip and palate treatment over the centuries – a historical view. Ann Acad Medicae Silesiensis. 2017;(71):399–406.
2. Bellis TH, Wohlgemuth B. The Incidence of Cleft Lip and Palate Deformities in the South-east of Scotland (1971-1990). Br J Orthod [Internet]. 1999 Jun 16;26(2):121–5. Available from: http://www.tandfonline.com/doi/full/10.1093/ortho/26.2.121
3. Vallino-Napoli LD, Riley MM, Halliday J. An Epidemiologic Study of Isolated Cleft Lip, Palate, or Both in Victoria, Australia from 1983 to 2000. Cleft Palate-Craniofacial J [Internet]. 2004 Mar 15;41(2):185–94. Available from: https://pubmed.ncbi.nlm.nih.gov/14989685/
4. Kim S, Kim WJ, Oh C, Kim JC. Cleft lip and Palate Incidence Among the Live Births in the Republic of Korea. J Korean Med Sci [Internet]. 2002;17(1):49–52. Available from: https://jkms.org/DOIx.php?id=10.3346/jkms.2002.17.1.49
5. Kummer A. Anatomy and Physiology of the orofacial structures and velopharyngeal valve in Cleft palate and craniofacial anomalies: Effects on Speech and Resonance. 2nd ed. New York: Thomas Delimar Learning; 2008. 2–35 p.
6. Prahl C, Kuijpers-Jagtman AM, Van 'T Hof MA, Prahl-Andersen B. A randomised prospective clinical trial into the effect of infant orthopaedics on maxillary arch dimensions in unilateral cleft lip and palate (Dutchcleft). Eur J Oral Sci [Internet]. 2001 Oct;109(5):297–305. Available from: http://doi.wiley.com/10.1034/j.1600-0722.2001.00056.x
7. Alzain I, Batwa W, Cash A, Murshid ZA. Presurgical cleft lip and palate orthopedics: an overview. Clin Cosmet Investig Dent [Internet]. 2017 May;Volume 9:53–9. Available from: https://www.dovepress.com/presurgical-cleft-lip-and-palate-orthopedics-an-overview-peer-reviewed-article-CCIDE
8. Retnakumari N, Divya S, Meenakumari S, Ajith PS. Nasoalveolar molding treatment in presurgical infant orthopedics in cleft lip and cleft palate patients. Arch Med Heal Sci [Internet]. 2014;2(1):36. Available from: http://www.amhsjournal.org/text.asp?2014/2/1/36/133804
9. Grayson BH, Maull D. Nasoalveolar Molding for Infants Born with Clefts of the Lip, Alveolus, and Palate. Semin Plast Surg [Internet]. 2005;19(04):294–301. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2005-925902
10. Altug AT. Presurgical Nasoalveolar Molding of Bilateral Cleft Lip and Palate Infants: An Orthodontist's Point of View. Turkish J Orthod [Internet]. 2017 Dec 22;30(4):118–25. Available from: https://turkjorthod.org/en/presurgical-nasoalveolar-molding-of-bilateral-cleft-lip-and-palate-infants-an-orthodontist-s-point-of-view-13911
11. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet [Internet]. 2009 Nov;374(9703):1773–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673609606954
12. Mosahebi A, Kangesu L. Cleft lip and palate. Surg [Internet]. 2006 Jan;24(1):33–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0263931906701740
13. Murthy PS, Deshmukh S, Bhagyalakshmi A, Srilatha K. Pre surgical nasoalveolar molding: changing paradigms in early cleft lip and palate rehabilitation. J Int oral Heal JIOH [Internet]. 2013 Apr;5(2):70–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24155594
14. Santiago PE, Schuster LA, Levy-Bercowski D. Management of the Alveolar Cleft. Clin Plast Surg [Internet]. 2014 Apr;41(2):219–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0094129814000029
15. Piekarczyk B, Młynarska-Zduniak E, Winiarska-Majczyno M. Rozszczep wargi i podniebienia. Poradnik dla rodziców [in Polish]. Warszawa: Wydawnictwo Learskie PZWL; 2003. 25–29 p.
16. Szeląg J, Penkala J, Mikulewicz M, Antoszewska J. Leczenie ortodontyczne rozszczepów [in Polish]. In: Matthews-Brzozowska T, editor. Rozszczepy wargi i podniebienia. Wrocław: Uniwersytet Medyczny we Wrocławiu; 2007. p. 50–7.
17. Tollefson T, Gere R. Presurgical Cleft Lip Management: Nasal Alveolar Molding. Facial Plast Surg [Internet]. 2007 May;23(2):113–22. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2007-979280

18. Szarejko K, Kuć J, Aleksandrowicz K, Gołębiewska M. The essence of kinesiotaping in cranio-mandibular and cranio--facial area. Literature review. Part II. Prosthodontics [Internet]. 2016 Dec 21;66(6):437–44. Available from: https://doi.org/10.5604/.1226739
19. Dawjee SM, Julyan JC, Krynauw JC. Lip tape therapy in patients with a cleft lip--a report on eight cases. SADJ [Internet]. 2014 Mar;69(2):62, 64–8, 70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24974519
20. Grayson BH, Shetye PR. Presurgical nasoalveolar moulding treatment in cleft lip and palate patients. Indian J Plast Surg [Internet]. 2009 Oct 15;42(S 01):S56–61. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0039-1699377
21. Wang Q, Zhou L, Zhao J-Z, Ko EW-C. An Extraoral Nasoalveolar Molding Technique in Complete Unilateral Cleft Lip and Palate. Plast Reconstr Surg Glob Open [Internet]. 2013 Jul;1(4):e26. Available from: http://journals.lww.com/01720096-201307000-00003
22. Chen Y-F, Liao Y-F. A modified nasoalveolar molding technique for correction of unilateral cleft nose deformity. J Cranio--Maxillofacial Surg [Internet]. 2015 Dec;43(10):2100–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1010518215003340
23. Grayson BH, Garfinkle JS. Early cleft management: The case for nasoalveolar molding. Am J Orthod Dentofac Orthop [Internet]. 2014 Feb;145(2):134–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0889540613009815
24. Sharma MP, Sandhu BH, Kumar MA. Presurgical nasoalveolar molding in unilateral cleft lip and palate patient. Indian J Dent Adv [Internet]. 2012;4(4):1024–9. Available from: http://rep.nacd.in/ijda/pdf/4.4.1024.pdf
25. Shetye PR, Grayson BH. NasoAlveolar molding treatment protocol in patients with cleft lip and palate. Semin Orthod [Internet]. 2017 Sep;23(3):261–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1073874617300233
26. Mishima K, Sugahara T, Mori Y, Sakuda M. Three-Dimensional Comparison between the Palatal Forms in Infants with Complete Unilateral Cleft Lip, Alveolus, and Palate (UCLP) with and without Hotz's Plate. Cleft Palate-Craniofacial J [Internet]. 1996 Jan 15;33(1):77–83. Available from: http://journals.sagepub.com/doi/10.1597/1545-1569_1996_033_0312_tdcbtp_2.3.co_2
27. Padovano WM, Skolnick GB, Naidoo SD, Snyder-Warwick AK, Patel KB. Long-Term Effects of Nasoalveolar Molding in Patients With Unilateral Cleft Lip and Palate: A Systematic Review and Meta-Analysis. Cleft Palate-Craniofacial J [Internet]. 2021 Apr 22;59(4):462–74. Available from: https://doi.org/10.1177/10556656211009702
28. Maull DJ, Grayson BH, Cutting CB, Brecht LL, Bookstein FL, Khorrambadi D, et al. Long-Term Effects of Nasoalveolar Molding on Three-Dimensional Nasal Shape in Unilateral Clefts. Cleft Palate-Craniofacial J [Internet]. 1999 Sep 15;36(5):391–7. Available from: http://journals.sagepub.com/doi/10.1597/1545-1569_1999_036_0391_lteonm_2.3.co_2
29. Lee CTH, Garfinkle JS, Warren SM, Brecht LE, Cutting CB, Grayson BH. Nasoalveolar Molding Improves Appearance of Children with Bilateral Cleft Lip–Cleft Palate. Plast Reconstr Surg [Internet]. 2008 Oct;122(4):1131–7. Available from: https://journals.lww.com/plasreconsurg/Fulltext/2008/10000/Nasoalveolar_Molding_Improves_Appearance_of.18.aspx
30. Lee CTH, Grayson BH, Cutting CB, Brecht LE, Lin WY. Prepubertal Midface Growth in Unilateral Cleft Lip and Palate following Alveolar Molding and Gingivoperiosteoplasty. Cleft Palate-Craniofacial J [Internet]. 2004 Jul 1;41(4):375–80. Available from: https://doi.org/10.1597/03-037.1
31. Ringdahl L. The Long-term effect of nasoalveolar molding on midface Growth and nasolabial esthetics in complete unilateral cleft lip and palate patients [Internet]. Nova Southeastern University; 2011. Available from: https://www.proquest.com/openview/739693d20851f233f35a58b4c2b675f9/1?cbl=18750&pq-origsite=gscholar&parentSessionId=iaWMlERNQThZDCP%2BV2s%2BnNrmHCpMjFjWoUvdoEQRG8k%3D
32. Ma L, Hou Y, Liu G, Zhang T. Effectiveness of presurgical orthodontics in cleft lip and palate patients with alveolar bone grafting: A systematic review. J Stomatol Oral Maxillofac Surg [Internet]. 2021;122(1):13–7. Available from: https://www.sciencedirect.com/science/article/pii/S2468785520301737
33. Abbott MM, Meara JG. Nasoalveolar Molding in Cleft Care. Plast Reconstr Surg [Internet]. 2012 Sep;130(3):659–66. Available from: https://journals.lww.com/plasreconsurg/Fulltext/2012/09000/Nasoalveolar_Molding_in_Cleft_Care__Is_It.30.aspx
34. Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Cleft Palate J [Internet]. 1987 Jan;24(1):5–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3542303
35. Adali N, Mars M, Petrie A, Noar J, Sommerlad B. Presurgical orthopedics has no effect on archform in unilateral cleft lip and palate. Cleft Palate Craniofac J [Internet]. 2012 Jan;49(1):5–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21823827
36. Konst EM, Weersink-Braks H, Rietveld T, Peters H. An intelligibility assessment of toddlers with cleft lip and palate who received and did not receive presurgical infant orthopedic treatment. J Commun Disord [Internet]. 2000;33(6):483–501. Available from: https://www.sciencedirect.com/science/article/pii/S0021992400000356

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REVIEW ARTICLE

Early extubation protocol post-coronary artery bypass graft & open heart surgery

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Abstract

Fast-tracking in cardiac care refers to the complex intervention including early extubation, care during anesthesia, mobilization and hospital discharge to reduce perioperative morbidity, costs, and length of stay in the intensive care unit and the hospital. This review was designed to evaluate early extubation protocols, the differences in early and late extubation, the safety and efficacy of early extubation among the patients in surgical intensive care after coronary artery bypass graft (CABG) surgery. The analyzed studies showed many significant differences in the mortality and postoperative complications of time-directed extubation practices and low dose-based general anesthesia in patients with low to moderate risk undergoing early extubation (fast-track) and the conventional care methods. Different fast-track interventions could diminish extubation time, costs, and the length of hospital stay. However, several factors including patient's stay in the intensive therapy ward vs general ward, patient selection, skills and experience of the staff, and fast-track anesthesia methods could be considered to perform safe fast-tracking in patients undergoing cardiac surgery. On the other hand, to achieve this safety for high-risk cardiosurgery patients multidisciplinary coordination is needed.

Keywords: early extubation · valve surgery · coronary artery bypass surgery

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Introduction

Post-operative outcome improvement directly depends on fundamental alterations in anesthesia and surgery, extracorporeal perfusion methods and peri-operative care systems [1-2]. Fast-track cardiac care, also called early extubation, has been first described by Prakash et al. in 1977 [3]. Fast-tracking in cardiac care refers to the complex intervention including early extubation, care during anesthesia, mobilization and hospital discharge to reduce perioperative morbidity, costs, and length of stay in the intensive care unit and the hospital. Efforts have continued to reduce the risk of respiratory complications due to tracheal intubation, mechanical ventilation and other risk factors including age and several thoracic surgical approaches [1, 4-8] The main goal of the majority of fast-track protocols was to optimize the length of patients' stay (LOS) and to reduce total costs following the coronary artery bypass graft (CABG) surgery, by emphasizing on early and fast extubation at the surgical intensive care unit (SICU) [9-13].

Based on the Society of Thoracic Surgeons (STS) guidelines, a 6-hour time point is considered "early extubation" and "prolonged intubation" referred to the longer than 24 hours time points [14-17] There is an ongoing interest in early extubation due to prevent adverse effects associated with late extubation, as well as any extra costs [18-19] However, due to the heterogeneity in cardiac surgery patient populations, previously advocated practices and risk prediction protocols have not been very successful. There are some confusing points in terms of the increased complication rate time in CABG.

The aim of this review is to determine the effect of early intubation time on post-operative morbidity and mortality rate in patients undergoing general anesthesia following the valve and CABG surgery.

Material and methods

In this review study, we evaluated all articles published from the year 2000 to 2021 related to early extubation protocols post-coronary artery bypass graft and open-heart surgery. Articles were searched by one researcher in PubMed, Web of Science, Scopus, Google Scholar, Science Direct and Cochrane Library using the keywords "early extubation", "early extubation protocol", "coronary artery bypass graft" and "open heart surgery."

Results

A total of 296 articles were extracted in the initial search. After reviewing the abstracts of these articles, 76 articles were selected and their full texts were included in the analysis.

History of early extubation following major surgery

Fast-track cardiac care has been applied in most of the study population (123 of 142 adult patients) after or within 3 h following open-heart surgery [3]. The best candidates for this approach were the patients who have been given minimal fluids and had a decrease in the cardiac index and ventricular filling pressures [20]. They reported immediate extubation in 5/36 patients and an average time of 6 h for the remainder of that group. Other researchers presented successful extubation 8 hours after surgery [21-22]. In another article, the best candidates for early extubation were hemodynamically stable, had an alveolar-arterial gradient of < 150 mmHg, good donor liver function and no encephalopathy [23]. In a combined strategy including all levels of care for the early 48 h after liver transplantation, the time to extubation and LOS at ICU were shorter, without changes in staff and intraoperative protocols [24].

Fast-track in cardiac care

Fast-track cardiac care referred to the complex intervention including cardiac anesthesia care and the post-operative care with a special focus on early extubation after surgery to diminish hospital LOS and expenses [25-26] In conventional (not fast-track) care units, high-dose opioid-based anesthesia has been applied in cardiac surgery followed by overnight mechanical breathing support in ICU after cardiac surgery [25]. However, in the new fast-track care units mechanical breathing support is applied on the operating table or within hours after cardiac surgery via the time-directed protocols for breathing support removal [27]. A Cochrane review updated in 2016 included 28 trials with 4438 participants. Most participants have been considered to be at low to moderate risk of death after surgery. No differences in risk of mortality were observed between low-dose versus high-dose opioid-based general anesthesia groups (OR 0.53, 95% CI 0.25 to 1.12; 8 trials, 1994 participants, low level of evidence) within the first year of surgery. There were also no differences in risk of mortality between a time-directed extubation protocol versus conventional care (OR 0.80, 95% CI 0.45 to 1.45; 10 trials, 1802 participants, low level of evidence). They showed no significant differences in postoperative complications including myocardial infarction, stroke, and tracheal re-intubation between the mentioned study groups [27]. Application of low-dose opioid-based general anesthesia and time-directed extubation procedures using the fast-track method have major postoperative complications and mortality risk as well as conventional (not fast-track) method suggesting its safety for use in low to moderate risk patients [27].

Opinions for and against fast-track anesthesia

Among the advantages of fast-track anesthesia are improved graft blood flow, decreased complications from

mechanical ventilation, fewer chest radiographs, improved resource utilization patient comfort, and cost containment [28]. Disadvantages include the chance of failed extubation and re-operation. In addition, there is a lack of large prospective studies regarding the benefits of the fast-track approach [28] (see Table 1).

Some concerns have been reported regarding the increased rate of re-intubation and the risk for perioperative adverse effects after early extubation, particularly among old or high-risk patients [29-32]. The safety of early extubation after CABG has been shown in a community practice of 6446 CABG patients from 35 hospitals, aged 65 years and older with shorter hospital stays without any adverse effect on postoperative outcomes between 1995 to 1998 [33]. In a retrospective analysis of findings in 1,904 patients undergoing CABG with different intubation times after surgery including 0-6, 6-9, 9-12, 12-24, and over 24 hours, there was no increase in postoperative complications before 12 hours of intubation [34]. It has been reported that prolonged intubation time can be increased mortality and morbidity rate in CABG patients [25] [27, 35]. Shorter ICU and hospital LOS were observed in patients who extubated earlier after the operation.

Feasibility of fast-track approach in cardiac surgery

It has been reported that the fast-track approach could be feasible in both simple and complex surgical procedures in all age groups [26]. Although early extubation is a fundamental part of the fast-track approach, there is no universal definition of ”early” and currently it is referred to as 6-8 hours post-cardiac surgery) [26]. In a study of 197 pediatric patients the successful extubation rate was 61% in the operating room (OR) [42]. In another study, 67% of children were extubated in the OR following surgery for congenital heart disease or within 6 hours of admission to the ICU without complications [43]. The patient/parent satisfaction, the feasibility, and safety of the fast-track approach in cardiac surgery have been found in large-scale series of patients undergoing adult cardiac surgery [44]. In a retrospective study, the extubation rate of 73% was observed in the OR of 901 patients [45]. The findings of another study showed the extubation rate of 87% in OR as an ultra-fast track method in elective congenital cardiac surgery [46]. Mittnacht et al. showed 79% extubation rate in OR of 224 patients [47].

Discussion

There is considerable disagreement regarding the classification of fast-track and ultrafast-track techniques. Several time points between 1 and 24 hours are considered for extubation following cardiac surgery [48]. However, careful patient selection is considered a critical aspect of fast-tracking in many patients undergoing cardiac surgery [49-50]. Early or fast extubation could be lessened the length of ICU

Table 1. Summary of the pros and cons of the fast-track approaches

Ref.	Strategy for extubation	Findings
Bansal et al. [36]	Early extubation	Shorter ICU and hospital stay without any changes in re-intubation rates
Hiromoto et al. [37]	Early extubation in valve surgery	Patients after early extubation had shorter ICU and hospital stays
Quiroga et al. [38]	Early extubation and fast-track anesthesia	The decrease in the total cost for hospitalization, shorter duration of intensive care or avoiding the ICU
Taner et al. [39]	Early extubation and fast-track anesthesia	The decrease in total room charges, reduction in the number of chest radiographs and arterial blood sampling
Wu et al. [40]	Early extubation in patients with significant comorbidities	Common reasons for re-intubation after early extubation included respiratory insufficiency, pneumonia and reoperations
Glanemann et al. [41]	Early extubation	Increased re-intubation rate among patients extubated in the ICU versus patients extubated in the operating room

and hospital stays [51-52]. However, multidisciplinary and coordinated approaches seem necessary to safely accomplish fast-tracking. The benefits of fast-tracking in cardiac surgery have been proven by mostly retrospective analyses compared to prospective randomized studies [1, 30-31, 38, 48, 51] In a survey of 10 randomized clinical trials, early extubation compared to late extubation after cardiac surgery and the beneficial effect of fast-tracking as a reduced time of mechanical ventilation, shorter times of ICU and hospital stay, and resource usage was observed between the studies [53]. Hiromoto et al. evaluated the benefits and predictive value of early extubation in valve surgery needing long cardiopulmonary bypass and reported that early extubation was achieved in 44.3% of patients without increasing adverse events. Patients with early extubation had shorter ICU and hospital stays [37]. Ellis et al. demonstrated that after implementing a fast-track extubation protocol, the number of early extubations after cardiac surgery was successfully improved and fast-track extubation did not increase the re-intubation risk and other adverse events [54].

To prevent major cardiorespiratory complications, it is important to shorten the duration of intensive hemodynamic monitoring and endotracheal intubation after cardiac surgery, particularly in some higher-risk patients [55-56]. On the other hand, there is wide heterogeneity in pre-and intra-operative risk factors of fast-tracking and prolonged mechanical ventilation observed in developing countries [57]. In addition, the application of low-dose anesthesia following the early cessation method combined with the rapid reversal of muscle paralysis is considered the main aspect of intervention in some RCTs [49, 58-59]. Bansal et al. showed that early extubation could be associated with a shorter ICU and hospital stay with any changes in re-intubation rates [36]. Findings obtained from six clinical trials in a Cochrane Review showed no differences in the re-intubation rate, 30-day mortality and intensive care mortality in patients who were extubated within 8 hours after cardiac surgery [60]. Factors such as higher body surface space and extended ischemic times are considered prognostics of longer extubation times [61-62]. Other published studies did not display the relation between early extubation and higher rates of re-intubation [60, 63].

Conclusion

In conclusion, early extubation after cardiac surgeries reduces the length of ICU and hospital stay, reduces the total cost of care as well as the number of blood sampling and chest radiographs, however, it may increase the risk of re-intubation. No difference in mortality rate was observed due early extubation after cardiac surgeries.

Conflicts of interest

None.

References

1. Reis J, Mota J., Ponce P, Costa-Pereira A, Guerreiro M. Early extubation does not increase complication rates after coronary artery bypass graft surgery with cardiopulmonary bypass. Eur J Cardio-Thoracic Surg [Internet]. 2002 Jun;21(6):1026–30. Available from: https://academic.oup.com/ejcts/article-lookup/doi/10.1016/S1010-7940(02)00121-5
2. Grocott HP. Early extubation after cardiac surgery: The evolution continues. J Thorac Cardiovasc Surg [Internet]. 2017 Nov;154(5):1654–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022522317315659
3. Prakash O, Jonson B, Meij S, Bos E, Hugenholtz P, Nauta J, et al. Criteria for Early Extubation After Intracardiac Surgery in Adults. Anesth Analg [Internet]. 1977 Sep;56(5):703-708. Available from: http://journals.lww.com/00000539-197709000-00019
4. Kastanos N, Estopá Miró R, Marín Perez A, Xaubet Mir A, Agustí-Vidal A. Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long-term study. Crit Care Med [Internet]. 1983 May;11(5):362–7. Available from: http://journals.lww.com/00003246-198305000-00009
5. Quasha AL, Loeber N, Feeley TW, Ullyot DJ, Roizen MF. Postoperative respiratory care: a controlled trial of early and late extubation following coronary-artery bypass grafting. In: The Journal of the American Society of Anesthesiologists [Internet]. The American Society of Anesthesiologists; 1980. p. 142–8. Available from: https://watermark.silverchair.com/0000542-198002000-00007.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAv8wggL7BgkqhkiG9w0B-BwagggLsMIIC6AIBADCCAuEGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMowsNxcHhrsVS5ahDAgEQgIICsmPZ7fNFn-W5AM-mI3w18wqbiy2M63yZ
6. Gammon RB, Shin MS, Buchalter SE. Pulmonary Barotrauma in Mechanical Ventilation. Chest [Internet]. 1992 Aug;102(2):568–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S001236921634065X
7. Gibney RTN, Wilson RS, Pontoppidan H. Comparison of Work of Breathing on High Gas Flow and Demand Valve Continuous Positive Airway Pressure Systems. Chest [Internet]. 1982 Dec;82(6):692–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215369300

8. Fagon J-Y, Chastre J, Domart Y, Trouillet J-L, Pierre J, Darne C, et al. Nosocomial Pneumonia in Patients Receiving Continuous Mechanical Ventilation: Prospective Analysis of 52 Episodes with Use of a Protected Specimen Brush and Quantitative Culture Techniques. Am Rev Respir Dis [Internet]. 1989 Apr;139(4):877–84. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm/139.4.877
9. Higgins TL. Pro: early endotracheal extubation is preferable to late extubation in patients following coronary artery surgery. J Cardiothorac Vasc Anesth [Internet]. 1992 Aug;6(4):488–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1498307
10. Engelman RM, Rousou JA, Flack JE, Deaton DW, Humphrey CB, Ellison LH, et al. Fast-track recovery of the coronary bypass patient. Ann Thorac Surg [Internet]. 1994 Dec;58(6):1742–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/0003497594916748
11. Arom K V., Emery RW, Petersen RJ, Schwartz M. Cost-effectiveness and predictors of early extubation. Ann Thorac Surg [Internet]. 1995 Jul;60(1):127–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497595003568
12. Lee JH, Kim KH, VanHeeckeren DW, Murrell HK, Cmolik BL, Graber R, et al. Cost analysis of early extubation after coronary bypass surgery. Surgery [Internet]. 1996 Oct;120(4):611–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039606096800079
13. Konstantakos AK, Lee JH. Optimizing timing of early extubation in coronary artery bypass surgery patients. Ann Thorac Surg [Internet]. 2000 Jun;69(6):1842–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497500012480
14. Trouillet J-L, Combes A, Vaissier E, Luyt C-E, Ouattara A, Pavie A, et al. Prolonged mechanical ventilation after cardiac surgery: Outcome and predictors. J Thorac Cardiovasc Surg [Internet]. 2009 Oct;138(4):948–53. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022522309008125
15. Canver CC, Chanda J. Intraoperative and postoperative risk factors for respiratory failure after coronary bypass. Ann Thorac Surg [Internet]. 2003 Mar;75(3):853–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497502044934
16. Edwards FH, Clark RE, Schwartz M. Coronary artery bypass grafting: The Society of Thoracic Surgeons National Database experience. Ann Thorac Surg [Internet]. 1994 Jan;57(1):12–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/0003497594903581
17. Edwards FH, Grover FL, Shroyer ALW, Schwartz M, Bero J. The Society of Thoracic Surgeons National Cardiac Surgery Database: Current Risk Assessment. Ann Thorac Surg [Internet]. 1997 Mar;63(3):903–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497597000179
18. Moran JL, Peisach AR, Solomon PJ, Martin J. Cost Calculation and Prediction in Adult Intensive Care: A Ground-up Utilization Study. Anaesth Intensive Care [Internet]. 2004 Dec 14;32(6):787–97. Available from: http://journals.sagepub.com/doi/10.1177/0310057X0403200610
19. Cheng DCH, Karski J, Peniston C, Raveendran G, Asokumar B, Carroll J, et al. Early Tracheal Extubation after Coronary Artery Bypass Graft Surgery Reduces Costs and Improves Resource Use. Anesthesiology [Internet]. 1996 Dec 1;85(6):1300-1310. Available from: https://pubs.asahq.org/anesthesiology/article/85/6/1300/35963/Early-Tracheal-Extubation-after-Coronary-Artery
20. Rossaint R, Slama K, Jaeger M, Konrad M, Pappert D. Fluid restriction and early extubation for successful liver transplantation. In: Transplantation proceedings. 1990. p. 1533–4.
21. Mandell MS, Lockrem J, Kelley SD. Immediate Tracheal Extubation After Liver Transplantation: Experience of Two Transplant Centers. Anesth Analg [Internet]. 1997;84(2). Available from: https://journals.lww.com/anesthesia-analgesia/Fulltext/1997/02000/Immediate_Tracheal_Extubation_After_Liver.3.aspx
22. Mandell MS, Lockrem J, Kelley SD. Immediate Tracheal Extubation After Liver Transplantation: Experience of Two Transplant Centers. Surv Anesthesiol [Internet]. 1998;42(1). Available from: https://journals.lww.com/surveyanesthesiology/Fulltext/1998/02000/Immediate_Tracheal_Extubation_After_Liver.18.aspx
23. Neelakanta G, Sopher M, Chan S, Pregler J, Steadman R, Braunfeld M, et al. Early tracheal extubation after liver transplantation. J Cardiothorac Vasc Anesth [Internet]. 1997;11(2):165–7. Available from: https://www.sciencedirect.com/science/article/pii/S105307709790207X
24. Plevak DJ, Torsher LC. Fast tracking in liver transplantation. Liver Transplant Surg [Internet]. 1997 Jul;3(4):447–8. Available from: https://onlinelibrary.wiley.com/doi/10.1002/lt.500030419
25. Zhu F, Lee A, Chee Y. Fast-track cardiac care for adult cardiac surgical patients. Cochrane Database Syst Rev [Internet]. 2012;10. Available from: https://www.annals.in/text.asp?2010/13/2/92/62930
26. Mittnacht AJC, Hollinger I. Fast-tracking in pediatric cardiac surgery-the current standing. Ann Card Anaesth [Internet]. 2010;13(2):92. Available from: https://www.annals.in/text.asp?2010/13/2/92/62930
27. Wong W-T, Lai VK, Chee YE, Lee A. Fast-track cardiac care for adult cardiac surgical patients. Cochrane Database Syst Rev [Internet]. 2016 Sep 12;2016(9). Available from: http://doi.wiley.com/10.1002/14651858.CD003587.pub3

28. Aniskevich S. Fast track anesthesia for liver transplantation: Review of the current practice. World J Hepatol [Internet]. 2015;7(20):2303. Available from: http://www.wjgnet.com/1948-5182/full/v7/i20/2303.htm
29. Gravlee GP. On aging, fast-tracking, and derailment in CABG patients. J Cardiothorac Vasc Anesth [Internet]. 1998 Aug;12(4):379–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9713721
30. London MJ, Shroyer LA, Coll JR, MaWhinney S, Fullerton DA, Hammermeister KE, et al. Early Extubation following Cardiac Surgery in a Veterans Population. Anesthesiology [Internet]. 1998 Jun 1;88(6):1447–58. Available from: https://pubs.asahq.org/anesthesiology/article/88/6/1447/36924/Early-Extubation-following-Cardiac-Surgery-in-a
31. London MJ, Shroyer LA, Coll JR, MaWhinney S, Fullerton DA, Hammermeister KE, et al. Early Extubation Following Cardiac Surgery in a Veterans Population. Surv Anesthesiol [Internet]. 1999;43(3). Available from: https://journals.lww.com/survey-anesthesiology/Fulltext/1999/06000/Early_Extubation_Following_Cardiac_Surgery_in_a.4.aspx
32. Higgins TL. Safety issues regarding early extubation after coronary artery bypass surgery. J Cardiothorac Vasc Anesth [Internet]. 1995 Oct;9(5 Suppl 1):24–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8562899
33. Guller U, Anstrom KJ, Holman WL, Allman RM, Sansom M, Peterson ED. Outcomes of early extubation after bypass surgery in the elderly. Ann Thorac Surg [Internet]. 2004 Mar;77(3):781–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497503019015
34. Kotfis K, Szylińska A, Listewnik M, Lechowicz K, Kosiorowska M, Drożdżal S, et al. Balancing intubation time with postoperative risk in cardiac surgery patients – a retrospective cohort analysis. Ther Clin Risk Manag [Internet]. 2018 Nov;Volume 14:2203–12. Available from: https://www.dovepress.com/balancing-intubation-time-with-postoperative-risk-in-cardiac-surgery-p-peer-reviewed-article-TCRM
35. Walthall H, Robson D, Ray S. Do any preoperative variables affect extubation time after coronary artery bypass graft surgery? Hear Lung [Internet]. 2001 May;30(3):216–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0147956301125641
36. Bansal S, Thai HM, Hsu CH, Sai-Sudhakar CB, Goldman S, Rhenman BE. Fast Track Extubation Post Coronary Artery Bypass Graft: A Retrospective Review of Predictors of Clinical Outcomes. World J Cardiovasc Surg [Internet]. 2013;03(02):81–6. Available from: http://www.scirp.org/journal/doi.aspx?DOI=10.4236/wjcs.2013.32014
37. Hiromoto A, Maeda M, Murata T, Shirakawa M, Okamoto J, Maruyama Y, et al. Early extubation in current valve surgery requiring long cardiopulmonary bypass: Benefits and predictive value of preoperative spirometry. Hear Lung [Internet]. 2020 Nov;49(6):709–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0147956320303137
38. Quiroga M, Rodríguez MG, Montalván C, Abarca J, Viñuela M, Cavallieri S, et al. Trends in mechanical ventilation and immediate extubation after liver transplantation in a single center in Chile. Transplant Proc [Internet]. 2004 Jul;36(6):1683–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0041134504007493
39. Taner CB, Willingham DL, Bulatao IG, Shine TS, Peiris P, Torp KD, et al. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. Liver Transplant [Internet]. 2012 Mar;18(3):361–9. Available from: https://onlinelibrary.wiley.com/doi/10.1002/lt.22459
40. Wu J, Rastogi V, Zheng S-S. Clinical practice of early extubation after liver transplantation. Hepatobiliary Pancreat Dis Int [Internet]. 2012 Dec;11(6):577–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1499387212602288
41. Glanemann M, Langrehr J, Kaisers U, Schenk R, Müller A, Stange B, et al. Postoperative tracheal extubation after orthotopic liver transplantation. Acta Anaesthesiol Scand [Internet]. 2001 Mar;45(3):333–9. Available from: http://doi.wiley.com/10.1034/j.1399-6576.2001.045003333.x
42. Barash PG, Lescovich F, D. Katz J, Talner NS, Stansel HC. Early Extubation Following Pediatric Cardiothoracic Operation: A Viable Alternative. Ann Thorac Surg [Internet]. 1980;29(3):228–33. Available from: https://www.sciencedirect.com/science/article/pii/S0003497510618723
43. Heard GG, Lamberti JJ, Park SM, Waldman JD, Waldman J. Early extubation after surgical repair of congenital heart disease. Crit Care Med [Internet]. 1985;13(10):830–2. Available from: http://europepmc.org/abstract/MED/4028752
44. Cheng DCH, Karski J, Peniston C, Asokumar B, Raveendran G, Carroll J, et al. Morbidity outcome in early versus conventional tracheal extubation after coronary artery bypass grafting: A prospective randomized controlled trial. J Thorac Cardiovasc Surg [Internet]. 1996;112(3):755–64. Available from: https://www.sciencedirect.com/science/article/pii/S0022522396700624
45. Neirotti RA, Jones D, Hackbarth R, Paxson Fosse G. Early extubation in congenital heart surgery. Hear Lung Circ [Internet]. 2002;11(3):157–61. Available from: https://www.sciencedirect.com/science/article/pii/S1443950602901411
46. Vricella LA, Dearani JA, Gundry SR, Razzouk AJ, Brauer SD, Bailey LL. Ultra fast track in elective congenital cardiac surgery. Ann Thorac Surg [Internet]. 2000;69(3):865–71. Available from: https://www.sciencedirect.com/science/article/pii/S0003497599013065
47. Mittnacht AJC, Thanjan M, Srivastava S, Joashi U, Bodian C, Hossain S, et al. Extubation in the operating room after congenital heart surgery in children. J Thorac Cardiovasc Surg [Internet]. 2008;136(1):88–93. Available from: https://www.sciencedirect.com/science/article/pii/S0022522307020338

48. Totonchi Z, Azarfarin R, Jafari L, Alizadeh Ghavidel A, Baharestani B, Alizadehasl A, et al. Feasibility of On-table Extubation After Cardiac Surgery with Cardiopulmonary Bypass: A Randomized Clinical Trial. Anesthesiol Pain Med [Internet]. 2018 Sep 24;In Press(In Press). Available from: https://brief.land/aapm/articles/80158.html
49. Sullivan BL. Con: Early Extubation in the Operating Room Following Cardiac Surgery. Semin Cardiothorac Vasc Anesth [Internet]. 2012 Jul 22;16(4):187–9. Available from: https://doi.org/10.1177/1089253212452343
50. Serrano N, García C, Villegas J, Huidobro S, Henry CC, Santacreu R, et al. Prolonged Intubation Rates After Coronary Artery Bypass Surgery and ICU Risk Stratification Score. Chest [Internet]. 2005;128(2):595–601. Available from: https://www.sciencedirect.com/science/article/pii/S0012369215504017
51. Singh KE, Baum VC. Pro: Early Extubation in the Operating Room Following Cardiac Surgery in Adults. Semin Cardiothorac Vasc Anesth [Internet]. 2012 Jul 13;16(4):182–6. Available from: https://doi.org/10.1177/1089253212451150
52. Bainbridge D, Cheng D. Current evidence on fast track cardiac recovery management. Eur Hear J Suppl [Internet]. 2017 Jan 1;19(suppl_A):A3–7. Available from: https://doi.org/10.1093/eurheartj/suw053
53. Meade MO, Guyatt G, Butler R, Elms B, Hand L, Ingram A, et al. Trials Comparing Early vs Late Extubation Following Cardiovascular Surgery. Chest [Internet]. 2001;120(6, Supplement):445S-453S. Available from: https://www.sciencedirect.com/science/article/pii/S0012369215500020
54. Ellis MF, Pena H, Cadavero A, Farrell D, Kettle M, Kaatz AR, et al. Reducing Intubation Time in Adult Cardiothoracic Surgery Patients With a Fast-track Extubation Protocol. Crit Care Nurse [Internet]. 2021 Jun 1;41(3):14–24. Available from: https://doi.org/10.4037/ccn2021189
55. Mirinejad M, Azarfarin R, Asl AA. Cisatracurium in cardiac surgery - continuous infusion vs. bolus administration. Middle East J Anaesthesiol [Internet]. 2007;19(3):563–72. Available from: http://europepmc.org/abstract/MED/18044284
56. Svircevic V, Nierich AP, Moons KGM, Brandon Bravo Bruinsma GJ, Kalkman CJ, van Dijk D. Fast-Track Anesthesia and Cardiac Surgery: A Retrospective Cohort Study of 7989 Patients. Anesth Analg [Internet]. 2009;108(3). Available from: https://journals.lww.com/anesthesia-analgesia/Fulltext/2009/03000/Fast_Track_Anesthesia_and_Cardiac_Surgery__A.12.aspx
57. Iezzi F, di Summa M, Del Sarto P, Munene J. Fast-Track Extubation in Pediatric Cardiothoracic Surgery in Developing Countries. J Card Crit Care TSS [Internet]. 2017 Aug 29;01(01):021–3. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0037-1604334
58. Bajwa SJS, Kaur J, Khanna M. Changing anesthesia trends in cardiothoracic surgeries: A fast changing perspective. Anaesthesia, Pain Intensive Care [Internet]. 2016;20. Available from: http://www.apicareonline.com/wordpress/wp-content/uploads/2016/Oct/25A==RA-Changing anaesthesia trends in cardiothoracic surgeries-1.pdf
59. van Mastrigt GAPG, Joore MA, Nieman FHM, Severens JL, Maessen JG. Health-related quality of life after fast-track treatment results from a randomized controlled clinical equivalence trial. Qual Life Res [Internet]. 2010;19(5):631–42. Available from: https://doi.org/10.1007/s11136-010-9625-5
60. Hawkes CA, Dhileepan S, Foxcroft DR. Early extubation for adult cardiac surgical patients. Cochrane Database Syst Rev [Internet]. 2003;(4). Available from: https://doi.org//10.1002/14651858.CD003587
61. El Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J [Internet]. 2006 Sep 1;28(3):588 LP – 595. Available from: http://erj.ersjournals.com/content/28/3/588.abstract
62. Parlow JL, Ahn R, Milne B. L'obésité est un facteur de risque d'échec de l'extubation "précoce" à la suite d'un pontage aorto-coronarien. Can J Anesth [Internet]. 2006;53(3):288–94. Available from: https://doi.org/10.1007/BF03022217
63. Butler J, Chong GL, Pillai R, Westaby S, Rocker GM. Early extubation after coronary artery bypass surgery: effects on oxygen flux and haemodynamic variables. J Cardiovasc Surg (Torino) [Internet]. 1992;33(3):276–80. Available from: http://europepmc.org/abstract/MED/1601908

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REVIEW ARTICLE

Positive affect, well-being and the human conserved transcriptional response to adversity: a descriptive review

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Abstract

The theoretical and philosophical foundations of human well-being are well-described in psychology research. Within the construct of well-being, psychologists distinguish eudemonic positive affect and hedonic positive affect, although they are not only nor mutually exclusive approaches. Empirical findings demonstrate a correlation between the general positive affect and favorable health outcomes. Recent discoveries also show a biological pattern, which underlines the correlation. Thanks to describing the conserved transcriptional response to adversity (CTRA) mechanism, a new direction of research is emerging, exploring a relationship between profile of gene expression in immune cells and positive affect.

Keywords: well-being · eudemonic positive affect · hedonic positive affect · CTRA

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Introduction

While the injurious effects of chronic stress on the human body are well-known and described in the literature [1], the question of the impact of positive psychological processes on health still requires thorough investigation. Physiological mechanisms that underlie the correlation between positive affect and improved health results are particularly underdescribed. In recent studies the evidence is becoming apparent that there is a explicit link between positive affect and health involving reduced psychobiological activation of immune, neuroendocrine, autonomic and inflammatory pathways [2].

Positive affect, defined as experiencing emotional states which are positive in valence, can be distinguished

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between hedonic affect and eudaimonic affect. Hedonic positive affect describes experiencing positive feelings such as happiness, contentment, pleasure with low intensity of negative emotions and high life satisfaction. Eudaimonic positive affect describes also emotions such as vitality, curiosity and engagement that accompanies the movement towards one's potential, beyond simple self-gratification [3]. Experiencing eudaimonic/hedonic positive affect translates into the person's eudaimonic/hedonic well-being (respectively). Hedonic versus eudaimonic well-being has been found to be associated with differing inflammatory gene expression profiles in leukocytes from healthy individuals [4]. Similar in their affective and behavioral correlates, hedonia and eudaimonia are seen to have highly divergent transcriptome profiles, namely, they differ in up-regulated expression of proinflammatory genes, down-regulated expression of genes involved in antibody synthesis, and down-regulated expression of genes mediating type I IFN responses [4].

The aim of this paper is to present research that has been conducted so far in the field of positive affect and its link with psychobiological processes in human body. We provide a closer look into the literature to determine a body of existing knowledge and reveal interpretable patterns and trends in a collective field of physiology and psychology.

Materials and methods

To find studies for inclusion in this review, we searched PubMed and Web of Science. Searches were narrowed down to human studies both in English and Polish language. The search was conducted by applying the following terms: "conserved transcriptional response to adversity," "positive affect," "eudaimonic well-being," "hedonic well-being." Also, we screened the reference lists of selected publications for additional sources.

Results

The search retrieved 38 full text articles. After screening, 12 articles were included in the analysis.

Discussion

The CTRA mechanism

Conserved transcriptional response to adversity (CTRA) is a physiological pattern, arbitrated by the sympathetic nervous system "fight-or-flight" response. Within the pattern, upregulated expression of genes involved in inflammation and downregulated expression of genes involved in Type I interferon responses, is observed [5]. When a person is exposed to prolong hostile environmental conditions (such as loss, trauma, etc.) central nervous system is affected. The "fight-or-flight" stress response is activated from the sympathetic nervous system and it is followed by releasing a neurotransmitter, which is norepinephrine. These signals result in the activation of intracellular second messenger systems which have different effect on numerous transcription control pathways. At the time, the upregulated transcription of pro-inflammatory genes and downregulated transcription of Type I interferon antiviral genes, is observed [5]. Teleological analyses proposed that the CTRA's adaptive implication is that it turns the fundamental anti-microbial stan of the immune system away from its baseline condition of counteracting viral infections (also other intracellular pathogens, which are mediated by Type I interferons and cellular immune responses) and directs the system toward a more pro-inflammatory activity that would give an optimum level of defense against bacterial infections and tissue damage related to injure wounds [6]. In ancestorial times, when threat experiences were intense but temporary, activation of such a molecular defense by the sympathetic nervous system (in response to potential or perceived threat) guaranteed a mechanism for expecting changing microbial exposures and taking advantage of an impact of microbial exposure. Nowadays, when a human being is under a circumstance of more chronic low-grade threat, the CRTA pattern, by promoting chronic low-grade inflammation, seems to be conducive to the development of inflammation-related diseases (e.g. cardiovascular disease, neurodegenerative disease, neoplastic disease) [5]. In the studies presented below, when mentioning examination of the CTRA mechanism, gene expression levels were assessed in peripheral blood samples, and it is noteworthy that all analyses were conducted at the UCLA Social Genomics Core Laboratory which makes the results highly comparable and reliable (as the same protocols and methods were use to analyse all of the blood samples).

CTRA and psychological dimensions

Fredrickson et. al [4] focused on the biological implications (changes in the CTRA gene expression) of hedonic and eudaimonic well-being in a group of 80 healthy Americans (35 to 64 years of age) and revealed a correlation between eudaimonia and decreased expression of the CTRA mechanism, the correlation between hedonic well-being and significant up-regulation of the CTRA mechanism as well as that CTRA transcriptome profile was not different as a function of overall well-being (hedonic plus eudaimonic). In this

research CTRA gene expression was significantly down-regulated in a group of individuals showing a relative dominance of eudaimonia vs. hedonia, therefore gene regulatory architecture of the response of individuals' immune system may be more sensitive to the eudaimonic well-being vs. hedonic well-being as a source of human happiness than are conscious experiences.

In order to verify whether the findings described above extended to non-Western cultures, Lee et. all [7] examined a group of 152 healthy Korean adults. Their outcomes were consistent with those published by Fredrickson et. al [4] and showed significant correlation between eudaimonic well-being and CTRA in the Korean cohort. Furthermore, they indicated that the correlation between eudaimonia and CTRA is evident to become higher with age.

A relationship between dispositional optimism (defined as one's personality trait which inclined them towards positive expectations) and CTRA gene expression has been examined [8]. In a sample of 114 male Japanese workers, it was found that individual differences in optimism were inversely associated with CTRA expression. The results are consistent with the outcomes published by Kitayama et al. [9], where general eudaimonic well-being was associated with lower CTRA gene expression while general hedonic well-being was associated with higher CTRA gene expression in a group of 106 male workers of a Japanese IT company.

These results, which describe the link between general eudaimonia with CTRA, are consistent with one of studies conducted among highly involved videogame players (those who present significantly strong engagement with virtual world) [10]. The researchers have shown that higher level of a gamer's eudemonic well-being is linked to lesser genomic dysregulation in CTRA mechanism and that the eudaimonia-CTRA correlation is strongest among the most highly involved players. The authors also performed more detailed follow-up analyses and investigated the social and psychological aspects of eudaimonia and their influence on CTRA mechanism. Consistent with the authors' hypothesis, their results showed a stronger association between social well-being with lessened expression of CTRA than with psychological well-being and the hedonia did not show statistical significance with the CTRA. The sample consisted of 56 avid online videogame players, which is a limitation, nevertheless it suggests that committed social activity may help reduce CTRA expression.

A study based on a similar notion, namely that prosocial behavior is linked to lifespan [11-12] and that might be mediated by the pathway which implicates changes in gene expression, which consequently may affect disease development (or resistance), examined changes in CTRA in 159 adults. They were randomly divided into 4 groups and for 4 weeks, they engaged in either prosocial behavior directed towards specific people, or prosocial behavior directed towards the world in general or self-focused kindness or a neutral control task [13]. As expected in a randomized study, kindness-to-world, kindness-to-other, kindness-to-self and the control groups showed no difference in average sex, race/ethnicity, age, current illness symptoms, nor the initial level of CTRA gene expression. The analyses showed significant decrease in CTRA gene expression in the kindness-to-other group over time. The decrease was not observed in any other group. This study adds to the body of research that points out the importance of the social well-being dimension of eudaimonia in the CTRA gene expression.

Slightly different outcomes were observed in a study of 18 volunteers (aged 50+), placed in a third-grade kindergarten classroom, where their task was to work with students on academic skill development (e.g. reading proficiency and math) for 9 months [14]. Analyses, which were conducted at the baseline and the 9-month follow-up, revealed the correlation between measure of individual decrease in CTRA mechanisms with the measure of individual increase in eudaimonia over time. It is necessary to point out that the social component of eudaimonia increased significantly from base level to the 9-month follow-up, while the psychological component demonstrated no significant change over time, and neither of the components correlated significantly with change over time in CTRA mechanism. Only total of social and psychological components of eudaimonia was prognostic for CTRA gene expression changes.

Another study which analyzed the link between eudaimonic well-being and CTRA, though from a different perspective, examined the strength of CTRA in relation to loneliness [15]. In this study loneliness, defined as social isolation, was a risk factor, while eudaimonic well-being was a resilience factor. Data was collected from 108 community-dwelling older adults (mean age 73), and contain blood samples and an assessment of loneliness and eudaimonic well-being via psychological scales. In separate analysis, the results showed up-regulation of CTRA gene expression in association with loneliness and down-regulation in association with eudaimonia. In joint analyses, loneliness' effect was fully abrogated while eudaimonia continued to be associated with CTRA down-regulation. The results were independent of behavioral and demographic health-related risk factors. Reviewing outcomes and conclusions of the studies, a question about the direction of the association appears. Nevertheless, a person with lower CTRA might be psychosomatically healthy in ways that enhance their social relations, hence also their eudaimonic well-being.

CTRA, affect and health implications

The CTRA pattern also has been found to be associated with adverse hematopoietic stem-cell transplantation (HCT) clinical outcomes. A group of 78 HCT recipients who differed with socioeconomic status (SES) were compared in terms of pretransplant leukocyte CTRA gene expression. Data compiled from peripheral blood mononuclear cells collected pre-HCT from low SES patients showed significant CTRA upregulation compared with paired HCT individuals of high SES [16]. According to the literature, individuals with low SES have higher likelihood of being depressed [17] and it is necessary to consider that in depression the positive affect is significantly reduced [18].

Chronic adversity and distress triggers cancer initiation, progression and cancer metastasis, also plays an unfavorable role for anti-tumor immune function and therapy response [19]. Due to that, relationships between cognitive behavioral stress management (CBSM), disease-free survival (DFS), and CTRA have been investigated among breast cancer patients. CBSM is an empirically-validated group-based psychosocial intervention which assures greater DFS vs. a control condition. It builds an individual's emotional skills (e.g. positive coping skills, a high sense of coping self-efficacy), which works in favor of positive affect. The research revealed that patients (n = 28) randomized to the CBSM group (10-weeks program) showed lesser change in CTRA gene expression, while patients randomized to the control group (n = 23) showed increased CTRA expression in 6-12-month period. What is more, greater 6-12 month CTRA increases were associated with shorter DFS over 8-15 years of follow-up [20].

Another study of breast cancer survivors confirms that eudaimonic positive affect may be a significant mechanism in interventions intended to enhance health in vulnerable groups. A group of 22 women completed self-report surveys and provided blood samples before and after a 6-week mindfulness meditation practice [21]. This study demonstrated that increases in eudaimonic positive affect were correlated with a rise in the inversely weighted CTRA subcomponent connected to antiviral response. Interestingly, changes in eudaimonic positive affect were not significantly associated with changes in the pro-inflammatory CTRA subcomponent. Also, the study indicated no significant association between hedonic positive affect, nor depressive syndromes with overall CTRA gene expression. Nevertheless, there are findings of Antoni et al. [22] which suggest that negative affect is related to the pro-inflammatory, but not the antiviral component of the CTRA among breast cancer survivors.

It is necessary to bear in mind that hedonia and eudaimonia are not reciprocally exclusive approaches to happiness. Both, eudaimonic well-being and hedonic well-being, have common origins (e.g. recognized social connections) [23] and can have an effect on each other [23], i.e., positive affect inclines people to find positive meaning [24-25] and finding positive meaning causes a growth of positive affect [26].

Conslusions

CTRA is a significant framework for an understanding of psychoneuroimmunology relationships. It links a micro-level biology of illness and health with a macro-level of psychosocial processes. A possible neuroimmunological mechanism involved in the interactions of immune function and social behavior is a dopamine signaling, as it plays an important role in behavioral and brain development [27].

There is a growing body of literature examining the link between well-being and CTRA gene expression. However, it is necessary to acknowledge limitations of the presented studies, which include small sample size, lack of control group in some studies, short duration of the studies and lack of extended follow-ups. It is necessary to conduct further research of the CTRA components and its psychological correlates in order to accurately understand the pathway between positive affect/well-being and the CTRA mechanism. The understanding of the association could be especially beneficial for clinical groups including patients with inflammation related diseases, as CTRA gene expression is indicative of greater expression of proinflammatory genes and hence greater inflammation process. Further research conducted in that field could be a promising support in the treatment process. At present, it is necessary to be careful in interpreting the link between CTRA expression and clinical health outcomes, as the majority of studies contain no measures of clinical health outcomes at all. Questions about other potential variables mediated in the process still need to be investigated, as for the time being, drawing more general conclusion is limited. Heretofore, we can conclude that there is no biological toxicity in experiencing overall well-being, and the various routes of experiencing positive affect/well-being have distinct biological correlates.

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Conflicts of interests

None.

References

1. Segerstrom SC, Miller GE. Psychological Stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601-630. Available from: https://pubmed.ncbi.nlm.nih.gov/15250815
2. Bower JE, Irwin MR. Mind–body therapies and control of inflammatory biology: A descriptive review. Brain Behav Immun. 2016 Jan;51:1-11. Available from: https://pubmed.ncbi.nlm.nih.gov/26116436
3. Ryff CD. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. J Pers Soc Psychol. 1989 Dec;57(6):1069-81. Available from: https://psycnet.apa.org/record/1990-12288-001
4. Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JMG, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci. 2013;110(33):13684-13689. Available from: https://pubmed.ncbi.nlm.nih.gov/23898182
5. Cole SW. The Conserved Transcriptional Response to Adversity. Curr Opin Behav Sci. 2019 Aug;28:31-37. Available from: https://pubmed.ncbi.nlm.nih.gov/31592179
6. Cole SW. Human social genomics. PLoS Genet. 2014 Aug; 10(8): e1004601. Available from: https://dx.plos.org/10.1371/journal.pgen.1004601
7. Lee S, Choi I, Choi E, Lee M, Kwon Y, Oh B, Cole SW. Psychological well-being and gene expression in Korean adults: The role of age. Psychoneuroendocrinology. 2020 Oct; 120:104785.Available from: https://pubmed.ncbi.nlm.nih.gov/32622293
8. Uchida Y, Kitayama S, Akutsu S, Park J, Cole S. Optimism and the Conserved Transcriptional Response to Adversity. Health Psychol. 2018 Nov; 37(11): 1077-1080. Available from: https://pubmed.ncbi.nlm.nih.gov/30221968
9. Kitayama S, Akutsu S, Uchida Y, Cole SW. Work, meaning, and gene regulation: Findings from a Japanese information technology firm. Psychoneuroendocrinology. 2016 Oct;72:175-81. Available from: https://pubmed.ncbi.nlm.nih.gov/27434635
10. Snodgrass JG, Lacy MG, Dengah II HJF, Polzer ER, Else RJ, Arevalo JMG, Cole SW. Positive Mental Well-Being and Immune Transcriptional Profiles in Highly Involved Videogame Players. Brain Behav Immun. 2019 Nov;82: 84-92. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0889159119304210
11. Brown SL, Brown RM. Connecting prosocial behavior to improved physical health: contributions from the neurobiology of parenting. Neurosci Biobehav Rev. 2015 Aug;55:1-17. Available from: https://pubmed.ncbi.nlm.nih.gov/25907371
12. Burr JA, Han SH, Tavares JL. Volunteering and cardiovascular disease risk: does helping others get “under the skin”?. Gerontologist. 2016 Oct;56(5):937-47. Available from: https://pubmed.ncbi.nlm.nih.gov/26035902
13. Nelson-Coffey KS, Fritz MM, Lyubomirsky S, Cole SW. Kindness in the blood: A randomized controlled trial of the gene regulatory impact of prosocial behavior. Psychoneuroendocrinology. 2017 Jul;81:8-13. Available from: https://pubmed.ncbi.nlm.nih.gov/28395185
14. Seeman T, Merkin SS, Goldwater D, Cole SW. Intergenerational mentoring, eudaimonic well-being and gene regulation in older adults: A pilot study. Psychoneuroendocrinology. 2020 Jan;111:104468. Available from: https://pubmed.ncbi.nlm.nih.gov/31589939
15. Cole SW, Levine ME, Arevalo JMG, Ma J, Weir DR, Crimmins ME. Loneliness, eudaimonia, and the human conserved transcriptional response to adversity. Psychoneuroendocrinology. 2015 Dec;62:11-7. Available from: https://pubmed.ncbi.nlm.nih.gov/26246388
16. Knight JM, Rizzo JD, Logan BR, Wang T, Arevalo JM, Ma J, Cole SW. Low socioeconomic status, adverse gene expression profiles, and clinical outcomes in hematopoietic stem cell transplant recipients. Clin Cancer Res 2016 Jan;22(1):69-78. Available from: https://pubmed.ncbi.nlm.nih.gov/26286914
17. Lorant V, Croux C, Weich S, Deliege D, Mackenbach J, Ansseau M. Depression and socio-economic risk factors: 7-year longitudinal population study. Brit J Psychiat. 2007 Apr;190:293-8. Available from: https://pubmed.ncbi.nlm.nih.gov/17401034
18. Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, Carrasco JL, Stahl S. The other face of depression, reduced positive affect: The role of catecholamines in causation and cure. J Psychopharmacol. 2007 Jul;21(5):461-71. Available from: https://pubmed.ncbi.nlm.nih.gov/17050654
19. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol. 2008 Aug;5(8):466-75. Available from: https://pubmed.ncbi.nlm.nih.gov/18493231
20. Antoni MH, Bouchard LC, Jacobs JM, Lechner SC, Jutagir DR, Gudenkauf LM, Carver CS, Lutgendorf S, Cole SW, Lippman M, Blomberg BB. Stress management, leukocyte transcriptional changes and breast cancer recurrence in a randomized trial: an exploratory analysis. Psychoneuroendocrinology. 2016 Dec;74:269-277. Available from: https://pubmed.ncbi.nlm.nih.gov/27689900

21. Boyle CC, Cole SW , Dutcherd JM, Eisenberger NI, Bower JE. Changes in eudaimonic well-being and the conserved transcriptional response to adversity in younger breast cancer survivors. Psychoneuroendocrinology. 2019 May;103:173-179. Available from: https://pubmed.ncbi.nlm.nih.gov/30703712
22. Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, Stagl J, Arevalo JMG, Cole SW. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012 Feb;71(4):366-72. Available from: https://pubmed.ncbi.nlm.nih.gov/22088795
23. King LA, Hicks JA. Positive affect and meaning in life: The intersection of hedonism and eudaimonia. In: Wong PTP editor. The human quest for meaning: Theories, research, and applications. 2nd ed. Routledge/Taylor & Francis Group; c2012. p. 125-142. Available from: https://books.google.pl/books?id=RHV_ioSkIJEC
24. King LA, Hicks JA, Krull JL, Del Gaiso AK. Positive affect and the experience of meaning in life. J Pers Soc Psychol. 2016 Feb; 90(1):179-196. Available from: https://www.researchgate.net/publication/7326319_Positive_affect_and_the_experience_of_meaning_in_life
25. Fredrickson BL, Cohn MA, Coffey KA, Pek J, Finkel SM. Open hearts build lives: Positive emotions, induced through loving-kindness meditation, build consequential personal resources. J Pers Soc Psychol [Internet]. 2008 Nov;95(5):1045-62. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/a0013262
26. Yamasaki K, Uchida K, Katsuma R. An intervention study of the effects of the coping strategy of “finding positive meaning” on positive affect and health. Int J Psychol. 2009 Aug;44(4):249-56. Available from: https://pubmed.ncbi.nlm.nih.gov/22029553
27. Kopec AM, Smith CJ, Bilbo SD. Neuro-Immune Mechanisms Regulating Social Behavior: Dopamine as Mediator? Trends Neurosci. 2019 May;42(5):337-348. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6486862

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REVIEW ARTICLE

Deep learning in pharmacology: opportunities and threats

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Abstract

Introduction: This review aims to present briefly the new horizon opened to pharmacology by the deep learning (DL) technology, but also to underline the most important threats and limitations of this method. **Material and Methods:** We searched multiple databases for articles published before May 2021 according to the preferred reported item related to deep learning and drug research. Out of the 267 articles retrieved, we included 49 in the final review **Results:** DL and other different types of artificial intelligence have recently entered all spheres of science, taking an increasingly central position in the decision-making processes, also in pharmacology. Hence, there is a need for better understanding of these technologies. The basic differences between AI (artificial intelligence), DL and ML (machine learning) are explained. Additionally, the authors try to highlight the role of deep learning methods in drug research and development as well as in improving the safety of pharmacotherapy. Finally, future directions of DL in pharmacology were outlined as well as possible misuses of it. **Conclusion:** DL is a promising and powerful tool for comprehensive analysis of big data related to all fields of pharmacology, however it has to be used carefully.

Keywords: deep learning · machine learning · artificial intelligence · drug research and development · pharmacology

Citation

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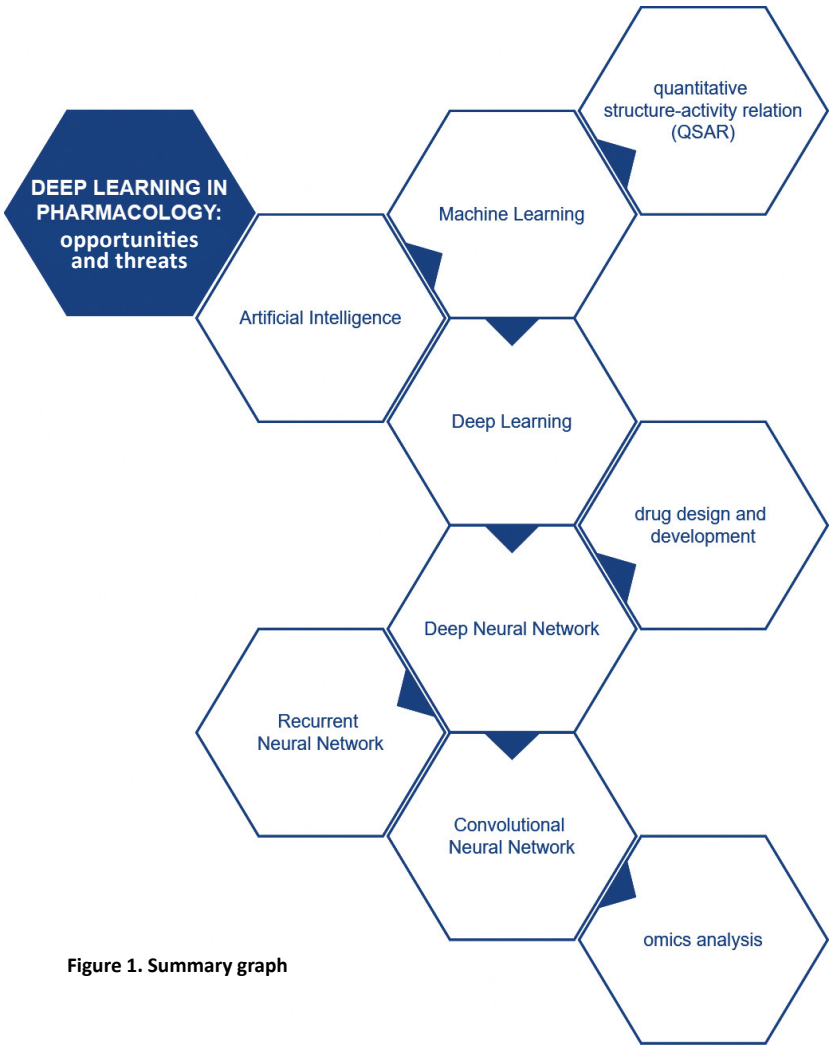

Figure 1. Summary graph

Introduction

Despite a widely accepted opinion that artificial intelligence (AI) era started with Alan Turing's publication of "Computing Machinery and Intelligence" in 1950 [1], discussion about that kind of human vision described with mathematical symbols appeared for the first time in the XVII century with works by Leibniz, Hobbes and Descartes. However, the practical implementation of AI into daily life is fairly new, as it began in the 1990s [2]. There are several popular terms used to describe AI-related new technologies entering recently in almost all spheres of sciences and everyday life: artificial intelligence, machine learning (ML) and deep learning (DL) [3-4]. Of the three, AI is the broadest concept, encompassing both ML and DL. The basic characteristic of all of these new technologies is big data management, which allows to find out specific correlation patterns, invisible for simple algorithms, and statistical evaluation with limited data. ML uses algorithmic models, which treat the data as an unknown and find generalizable predictive patterns, while statistical modeling assumes that the data is generated by a given random data model and draws population inferences from a sample [5-6].

On the other hand, DL, a subset of ML, structures algorithms in layers to create deep neural network with many hidden layers, which provide better pattern recognition and new possibilities in data mining [7-9]. Specifically, the aim of DL is to determine a mathematical function f that maps a number of inputs (x) to their corresponding outputs (y), e.g. $y = f(x)$. In other words, standard network architecture of neural networks contains an input layer, several hidden layers in between and an output layer. A set of training data, often called "batch" is fed forward through the network's layers and the output layer computes the loss function as the difference between the calculated prediction and the correct response. After that, loss error of the next operation is reduced and a backpropagation algorithm adjusts filter banks and learns the value of the parameter resulting in the best function approximation [9]. Recurrent neural networks, derived from feedforward networks, do not use limited size of context, which allows information to cycle as long as needed. This makes them useful in sequential data prediction such as language modelling [10].

Another network type is the convolutional neural network (CNN), which is widely used in systems that deal with image classification and computer vision in general. CNNs are composed of multiple types of hidden layers: convolutional layers, pooling layers and fully-connected layers. Like in the other network types, the input layer contains the input data, i.e. the pixel values of the image. The convolutional layer calculates the scalar product between the weights and the region connected to the input volume. The rectified linear unit (ReLU) applies an "elementwise" activation function such as sigmoid to previous layer's activation output. The pooling layer performs downsampling along input's spatial dimensionality, reducing the number of parameters within activation. The fully-connected layers will then attempt to produce scores for classification from the activations. This is only the base architecture model – as CNNs often deal with very complex image data, optimisations are often necessary [11]. Some new deep learning approaches incorporate fusion strategies into the deep learning architecture itself, creating fuzzy hidden layers. These layers are able to condense hundreds of inputs into a more manageable set. Fusion can offer major reduction in model complexity [12].

As Schmidhuber et al. suggested, the primary deficiency of most traditional ML methods as compared to DL methods, is that they have a limited ability to simulate a complicated approximation function and generalize to an unseen instance [9]. Usually, ML is used for supervised analysis and DL for more complex, unsupervised ones. Matter of fact, DL methods can be used both in supervised applications- for accurate prediction of one or more labels or outcomes associated with each data point (instead of a simple regression approaches), as well as in unsupervised (or 'exploratory') applications, where the goal is to summarize, explain or identify appropriate patterns in a dataset as a form of clustering. Moreover, DL methods may combine both of these approaches and propose feature oriented one, as a highly precise predictor [13].

ML and DL are widely used in daily life, e.g. to improve street traffic safety, in marketing research and, what is seen as a very controversial issue, to determine the voters' preferences [14]. Medicine as a science and clinical discipline is not an exception. DL method is a very promising tool in the diagnostic procedures (e.g. in pathomorphology and X-ray imaging) and results interpretation, but needs further research. For instance, Wang et al. analysed stained slides of lymph node slices to identify cancers, and found out that a pathologist had an error rate of about 3%, while the applied algorithm had about 6%. The pathologist did not produce any false positives but did have a number of false negatives. The algorithm had about twice the error rate of a pathologist, but the errors were not strongly correlated [14]. Academic institutions and start-ups alike are rapidly developing prototype technologies using the data of healthcare providers, individuals, and healthcare organizations', however the ethical implications, vulnerabilities and potential for misuse of such tools are still not taken seriously [15].

The value of algorithms proposed by DL methods is directly dependent on the quality and quantity of the entry data. It seems that a DL analytical platform which has got thousands of microscopic samples or X-ray images of lung changes during pneumonia or kidney cancer will unmistakably recognize the next one. However, recent controversies with face recognition technology (accurate only for faces of white men, whereas 20-30% recognition of Asian women's faces) raise new questions about practical usage of image recognition technologies [16]. Currently, these new technologies are present in almost all areas of medicine, including pharmacology. This review aims to present briefly the new horizon opened to pharmacology by the deep learning (DL) technology, but also to underline the most important threats and limitations of this method.

Material and methods

The PubMed, EMBASE and Cochrane Library were searched for articles published before May 2021 according to the preferred reported item related to deep learning and drug research. The following keywords were applied: artificial intelligence, deep learning, machine learning and drug research, research and development. Articles were included in the analysis based on their quality and journal rank.

Results

Out of the 267 articles retrieved, we included 49 in the final review. No statistical analysis was performed.

Discussion

DL in pharmacology

There are many different aspects of possible use of DL as a tool able to create predictive models and recognize complex patterns in big data sets in drug research and development. A serious challenge for DL technology is how to manage the huge amounts of data obtained by omics technologies (e.g. metabolomics, genomics, proteomics, glycomics) in order to support and improve personal approach of pharmacotherapy. In this context, an up to date DL method is successfully used in sequence analysis, genome wide association studies, transcriptomics, epigenomics, proteomics and metabolomics. It seems that the convolutional neural network (CNN) DL model is the most suitable for omics analysis as a tool with a transfer learning strategy (transferring prior knowledge from a source domain into a target domain) dealing with relatively small data sets. Using this, it is possible to detect single nucleotide polymorphism (SNP) to predict the relation between genetic variants and gene expression, as well as to predict regulatory motifs in the genome and promoter sequences in the gene [17-22].

Pharmacology as a multidisciplinary science is practically involved in every clinical discipline of medicine (e.g. in surgery via the use of analgesics, anesthetics and antibiotics), hence special attention should be paid to it. Drug discovery and development is a complex process involving many different techniques. Traditional ML methods have already been widely used by pharmacologists in quantitative structure-activity relation (QSAR) models (Fig. 2). However, DL algorithms in drug design and development are slowly becoming dominant due to improved feasibility of computational management of the enormous amounts of chemical data involved [23-28].

Generally, there are three types of DL networks used in drug discovery: CNN, RNN and DNN. So far, many DL models for preclinical research have been reported. They predict the drug-target interaction of novel drug molecules (drug design) with theirs absorption, distribution, metabolism, excretion, and toxicity (ADMET) [29]. Interesting DL models have been developed for drug discovery requiring 3D structure

for both ligand and target, known as AtomNet [30]. Thanks to them it is possible to predict binding affinity for a selective active compound. The next step of using DL models in drug discovery process was modelling of drug mechanism of action (MOA) using genetic profile activity relationship (GPAR) [31]. In order to generate more reliable MOA hypothesis, one can use GPAR to customize its training set to train MOA prediction models and to evaluate the model performances. An interesting example of using DL for prediction of the new drug molecules to be further tested in industrial environment was published by Sturm et al [32]. They found that evaluation of ExCAPE-DB, one of the largest open-source benchmark target prediction datasets, allows to evaluate target prediction models trained on public data and predict industrial QSAR, therefore it is usable in industrial drug discovery projects.

A major challenge is an attempt to use AI and DL in order to improve the safety of pharmacotherapy. A part from posing serious health hazards and generating enormous financial costs, dverse drug reactions (ADRs) are preventable. There is a hope that DL can help in much better and effective prediction and significant reduction of ADR [33]. Finally, optimal medication dosing can be also predicted by using appropriate, publicly available big data and deep reinforcement learning approach [34]. Prediction of optimal and safe treatment of patients is a completely new field for DL application. Nevertheless, new methods to recommend patient treatment and predict its outcome as well as to identify drug targets and predict drug response and interactions are being developed [35-37]. Another prospective in development of DL in pharmacology is personalization of pharmacotherapy. For instance, the genetic expression profile-based screening of appropriate therapeutics for cancer treatment sis already in development (OncoFinder algorithm) [38].

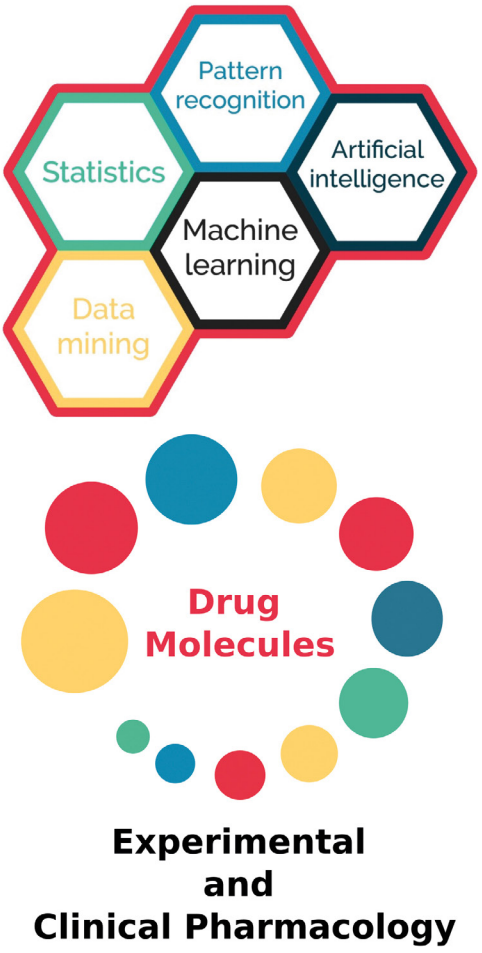

Figure 2. Deep learning in pharmacology

Conclusions

False interpretation of obtained data and misunderstanding of DL technology are the real and serious threats of using of DL as an advisor for personalizing of pharmacotherapy in context of type of drug and optimal dosing. Some of the most important pros and cons of DL are summarized in Table 1. Moreover, in basic biological research, measures of uncertainty help researchers distinguish between true regularities in the data and patterns that are false or uncertain. Two main types of uncertainties used in calculations are epistemic and aleatoric uncertainties [18]. Epistemic uncertainty is a measure of uncertainty concerning the model, including its structure and parameters. It is caused by the lack of sufficient training data, so that it can be reduced with better access to more data with better quality. In contrast, aleatoric uncertainty is a description of uncertainty of observations, due to the noise or missing parts in data. It diminishes with improvements in the measurement precision of the data [39].

Progress in decision making using deep learning is often set back by the fact that predicting results of a set of circumstances is much simpler than that based on a desirable outcome. There still remain many problems such as low interpretability of models and dealing with limited and mixed data in dynamic settings. Interpretability problems are particularly important as decision making in medicine is understandably averse to risk, and with low interpretability it is difficult to reason about the model and build trust in its correctness. While ML models also present some dangerous vulnerabilities, like misclassification of adversarial examples [40-41], there are constant improvements in this area [42-44]. Cooperation between human experts and DL-based systems seems to offer the best results for alleviating many problems [45-48]. Obviously, ethical issues are also extremely important in this context and can seriously restrict the use and publishing of very sensitive health related data [49].

Table 1. Pros and cons of machine and deep learning uses in medicine, according to Papernot et al. [15]

Pros	Cons
• wide application area and potential • better performance as compared to traditional methods • results and outcomes of DL analysis are new, previously unidentified • DL can reveal novel classes of treatable conditions • DL predictions can be evaluated by medical experts • Possible to process large amount of data (as in many previously untestable hypotheses) • higher degree of accuracy without human-biased extraction strategies • ability of DL to evaluate a huge amount of omic data that can be obtained from each cell, • in some situations missing data can be substituted with simulated data • deep learning models may have uniquely advantageous generalization properties • excellent perspective for further development with improvements in hardware and new theoretical approaches	• misdiagnosis by DL based on the tests by the physician (for suspected diagnosis) • difficulty of assigning a level of confidence to each prediction • limitations in some domains e.g. medical imaging, • user-friendly tools must be developed for deep learning to become commonplace • underdetermined, or ill-conditioned, problems are still a challenge for deep neural networks that require many training examples • it is often unclear whether simulations can produce sufficiently realistic data to produce reliable models • it is much easier to predict an outcome than to suggest an action to change the outcome • 'bias-variance' tradeoff • advancing deep learning takes a lot of computing power accruing from neural network training • issues involving legality and privacy resulting from using and sharing data • deep neural networks often make mistakes that are unlikely for humans to make

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Conflicts of interest

None.

References

1. Turing AM. Computing machinery and intelligence Mind 49 433-460. Mind. 1950;59(236):433–60.
2. Clark J. Why 2015 Was a Breakthrough Year in Artificial Intelligence [Internet]. Bloomberg. Europe Edition. 2015 [cited 2022 Aug 22]. Available from: https://www.bloomberg.com/news/articles/2015-12-08/why-2015-was-a-breakthrough-year-in-artificial-intelligence
3. Cukier K. Ready for robots? How to think about the future of AI [Internet]. Foreign Affairs. [cited 2022 Aug 22]. Available from: https://www.foreignaffairs.com/reviews/review-essay/2019-06-11/ready-robots
4. McCorduck P, Cfe C. Machines Who Think: A Personal Inquiry into the History and Prospects of Artificial Intelligence [Internet]. CRC Press; 2004. Available from: https://books.google.pl/books?id=r2C1DwAAQBAJ
5. Jang H, Park A, Jung K. Neural Network Implementation Using CUDA and OpenMP. In: 2008 Digital Image Computing: Techniques and Applications [Internet]. IEEE; 2008. p. 155–61. Available from: https://doi.org/10.1109/DICTA.2008.82
6. Bzdok D, Altman N, Krzywinski M. Statistics versus machine learning. Nat Methods [Internet]. 2018 Apr 3;15(4):233–4. Available from: https://doi.org/10.1038/nmeth.4642
7. Hollis KF, Soualmia LF, Séroussi B. Artificial Intelligence in Health Informatics: Hype or Reality? Yearb Med Inform [Internet]. 2019 Aug 16;28(01):003–4. Available from: https://doi.org/10.1055/s-0039-1677951
8. Lavecchia A. Machine-learning approaches in drug discovery: methods and applications. Drug Discov Today [Internet]. 2015 Mar;20(3):318–31. Available from: https://www.sciencedirect.com/science/article/pii/S1359644614004176

9. Schmidhuber J. Deep learning in neural networks: An overview. Neural Networks [Internet]. 2015;61:85–117. Available from: https://www.sciencedirect.com/science/article/pii/S0893608014002135
10. Mikolov T. Recurrent Neural Network based Language Model research paper [Internet]. 2010. Available from: http://www.fit.vutbr.cz/research/groups/speech/servite/2010/rnnlm_mikolov.pdf
11. O'Shea K, Nash R. An Introduction to Convolutional Neural Networks [Internet]. Cornell University. 2015 [cited 2023 Aug 22]. Available from: https://arxiv.org/abs/1511.08458
12. Price SR, Price SR, Anderson DT. Introducing Fuzzy Layers for Deep Learning. In: 2019 IEEE International Conference on Fuzzy Systems (FUZZ-IEEE) [Internet]. IEEE; 2019. p. 1–6. Available from: https://ieeexplore.ieee.org/document/8858790/
13. Cao C, Liu F, Tan H, Song D, Shu W, Li W, et al. Deep Learning and Its Applications in Biomedicine. Genomics Proteomics Bioinformatics [Internet]. 2018;16(1):17–32. Available from: https://www.sciencedirect.com/science/article/pii/S1672022918300020
14. Doucette J, Larson K, Cohen R. Conventional Machine Learning for Social Choice. Proc AAAI Conf Artif Intell [Internet]. 2015 Feb 16;29(1 SE-AAAI Technical Track: Game Theory and Economic Paradigms). Available from: https://ojs.aaai.org/index.php/AAAI/article/view/9294
15. Papernot N, McDaniel P, Sinha A, Wellman MP. SoK: Security and Privacy in Machine Learning. In: 2018 IEEE European Symposium on Security and Privacy (EuroS&P) [Internet]. IEEE; 2018. p. 399–414. Available from: https://ieeexplore.ieee.org/document/8406613/
16. Zou J, Schiebinger L. AI can be sexist and racist — it's time to make it fair. Nature [Internet]. 2018 Jul 18;559(7714):324–6. Available from: http://www.nature.com/articles/d41586-018-05707-8
17. Zhang L, Tan J, Han D, Zhu H. From machine learning to deep learning: progress in machine intelligence for rational drug discovery. Drug Discov Today [Internet]. 2017 Nov;22(11):1680–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1359644616304366
18. Ching T, Himmelstein DS, Beaulieu-Jones BK, Kalinin AA, Do BT, Way GP, et al. Opportunities and obstacles for deep learning in biology and medicine. J R Soc Interface [Internet]. 2018 Apr 4;15(141):20170387. Available from: https://royalsocietypublishing.org/doi/10.1098/rsif.2017.0387
19. Wang D, Khosla A, Gargeya R, Irshad H, Beck AH. Deep learning for identifying metastatic breast cancer. Cornell Univ [Internet]. 2016; Available from: https://arxiv.org/abs/1606.05718
20. Arnedo J, del Val C, de Erausquin GA, Romero-Zaliz R, Svrakic D, Cloninger CR, et al. PGMRA: a web server for (phenotype x genotype) many-to-many relation analysis in GWAS. Nucleic Acids Res [Internet]. 2013 Jul 1;41(W1):W142–9. Available from: https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkt496
21. Hill ST, Kuintzle R, Teegarden A, Merrill E, Danaee P, Hendrix DA. A deep recurrent neural network discovers complex biological rules to decipher RNA protein-coding potential. Nucleic Acids Res [Internet]. 2018 Sep 19;46(16):8105–13. Available from: https://academic.oup.com/nar/article/46/16/8105/5050624
22. Tripathi R, Patel S, Kumari V, Chakraborty P, Varadwaj PK. DeepLNC, a long non-coding RNA prediction tool using deep neural network. Netw Model Anal Heal Informatics Bioinforma [Internet]. 2016 Dec 10;5(1):21. Available from: http://link.springer.com/10.1007/s13721-016-0129-2
23. Alipanahi B, Delong A, Weirauch MT, Frey BJ. Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning. Nat Biotechnol [Internet]. 2015 Aug 27;33(8):831–8. Available from: http://www.nature.com/articles/nbt.3300
24. Date Y, Kikuchi J. Application of a Deep Neural Network to Metabolomics Studies and Its Performance in Determining Important Variables. Anal Chem [Internet]. 2018 Feb 6;90(3):1805–10. Available from: https://pubs.acs.org/doi/10.1021/acs.analchem.7b03795
25. Asakura T, Date Y, Kikuchi J. Application of ensemble deep neural network to metabolomics studies. Anal Chim Acta [Internet]. 2018 Dec;1037:230–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003267018302605
26. Svetnik V, Liaw A, Tong C, Culberson JC, Sheridan RP, Feuston BP. Random Forest: A Classification and Regression Tool for Compound Classification and QSAR Modeling. J Chem Inf Comput Sci [Internet]. 2003 Nov 1;43(6):1947–58. Available from: https://pubs.acs.org/doi/10.1021/ci034160g
27. Goh GB, Hodas NO, Vishnu A. Deep learning for computational chemistry. J Comput Chem [Internet]. 2017 Jun 15;38(16):1291–307. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcc.24764
28. Chen B, Sheridan RP, Hornak V, Voigt JH. Comparison of Random Forest and Pipeline Pilot Naïve Bayes in Prospective QSAR Predictions. J Chem Inf Model [Internet]. 2012 Mar 26;52(3):792–803. Available from: https://pubs.acs.org/doi/10.1021/ci200615h
29. Myint KZ, Xie X-Q. Ligand Biological Activity Predictions Using Fingerprint-Based Artificial Neural Networks (FANN-QSAR). In 2015. p. 149–64. Available from: http://link.springer.com/10.1007/978-1-4939-2239-0_9

30. Ma C, Wang L, Yang P, Myint KZ, Xie X-Q. LiCABEDS II. Modeling of Ligand Selectivity for G-Protein-Coupled Cannabinoid Receptors. J Chem Inf Model [Internet]. 2013 Jan 28;53(1):11–26. Available from: https://pubs.acs.org/doi/10.1021/ci3003914
31. Gray KA, Yates B, Seal RL, Wright MW, Bruford EA. Genenames.org: the HGNC resources in 2015. Nucleic Acids Res [Internet]. 2015 Jan 28;43(D1):D1079–85. Available from: http://academic.oup.com/nar/article/43/D1/D1079/2437320/Genenamesorg-the-HGNC-resources-in-2015
32. Sturm N, Mayr A, Le Van T, Chupakhin V, Ceulemans H, Wegner J, et al. Industry-scale application and evaluation of deep learning for drug target prediction. J Cheminform [Internet]. 2020 Dec 19;12(1):26. Available from: https://jcheminf.biomedcentral.com/articles/10.1186/s13321-020-00428-5
33. Basile AO, Yahi A, Tatonetti NP. Artificial Intelligence for Drug Toxicity and Safety. Trends Pharmacol Sci [Internet]. 2019 Sep;40(9):624–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165614719301427
34. Nemati S, Ghassemi MM, Clifford GD. Optimal medication dosing from suboptimal clinical examples: A deep reinforcement learning approach. In: 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) [Internet]. IEEE; 2016. p. 2978–81. Available from: http://ieeexplore.ieee.org/document/7591355/
35. Ferreira LLG, Andricopulo AD. ADMET modeling approaches in drug discovery. Drug Discov Today [Internet]. 2019 May;24(5):1157–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1359644618303301
36. Tsou LK, Yeh S-H, Ueng S-H, Chang C-P, Song J-S, Wu M-H, et al. Comparative study between deep learning and QSAR classifications for TNBC inhibitors and novel GPCR agonist discovery. Sci Rep [Internet]. 2020 Dec 8;10(1):16771. Available from: https://www.nature.com/articles/s41598-020-73681-1
37. Gao S, Han L, Luo D, Liu G, Xiao Z, Shan G, et al. Modeling drug mechanism of action with large scale gene-expression profiles using GPAR, an artificial intelligence platform. BMC Bioinformatics [Internet]. 2021 Dec 7;22(1):17. Available from: https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-020-03915-6
38. Aliper A, Plis S, Artemov A, Ulloa A, Mamoshina P, Zhavoronkov A. Deep Learning Applications for Predicting Pharmacological Properties of Drugs and Drug Repurposing Using Transcriptomic Data. Mol Pharm [Internet]. 2016 Jul 5;13(7):2524–30. Available from: https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.6b00248
39. Wen M, Zhang Z, Niu S, Sha H, Yang R, Yun Y, et al. Deep-Learning-Based Drug–Target Interaction Prediction. J Proteome Res [Internet]. 2017 Apr 7;16(4):1401–9. Available from: https://pubs.acs.org/doi/10.1021/acs.jproteome.6b00618
40. Gawehn E, Hiss JA, Schneider G. Deep Learning in Drug Discovery. Mol Inform [Internet]. 2016 Jan;35(1):3–14. Available from: https://onlinelibrary.wiley.com/doi/10.1002/minf.201501008
41. Baskin II, Winkler D, Tetko I V. A renaissance of neural networks in drug discovery. Expert Opin Drug Discov [Internet]. 2016 Aug 2;11(8):785–95. Available from: http://www.tandfonline.com/doi/full/10.1080/17460441.2016.1201262
42. Zeng B, Glicksberg BS, Newbury P, Chekalin E, Xing J, Liu K, et al. OCTAD: an open workspace for virtually screening therapeutics targeting precise cancer patient groups using gene expression features. Nat Protoc [Internet]. 2021 Feb 23;16(2):728–53. Available from: http://www.nature.com/articles/s41596-020-00430-z
43. Kendall A, Gal Y. What Uncertainties Do We Need in Bayesian Deep Learning for Computer Vision? [Internet]. Cornell University. 2017 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1703.04977v2
44. Kendall A, Gal Y, Cipolla R. Multi-Task Learning Using Uncertainty to Weigh Losses for Scene Geometry and Semantics [Internet]. Cornell University. 2017 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1705.07115
45. Szegedy C, Zaremba W, Sutskever I, Bruna J, Erhan D, Goodfellow I, et al. Intriguing properties of neural networks [Internet]. Cornell University. 2013 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1312.6199
46. Goodfellow IJ, Shlens J, Szegedy C. Explaining and Harnessing Adversarial Examples [Internet]. Cornell University. 2014 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1412.6572
47. Papernot N, McDaniel P, Sinha A, Wellman M. Towards the Science of Security and Privacy in Machine Learning [Internet]. Cornell University. 2016 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1611.03814v1
48. Xu W, Evans D, Qi Y. Feature Squeezing: Detecting Adversarial Examples in Deep Neural Networks [Internet]. Cornell University. 2017 [cited 2022 Aug 26]. Available from: https://arxiv.org/abs/1704.01155
49. Phillips A, Borry P, Shabani M. Research ethics review for the use of anonymized samples and data: A systematic review of normative documents. Account Res [Internet]. 2017 Nov 17;24(8):483–96. Available from: https://www.tandfonline.com/doi/full/10.1080/08989621.2017.1396896

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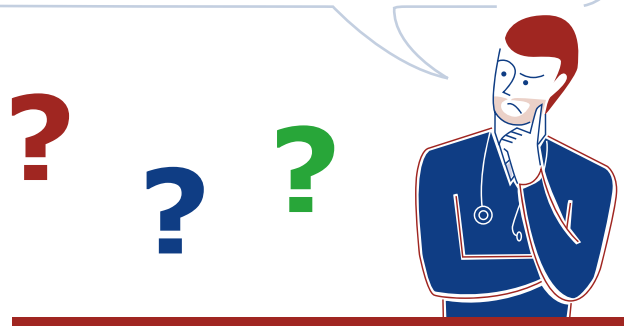

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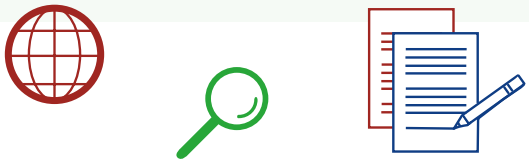

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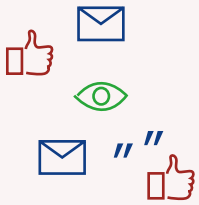

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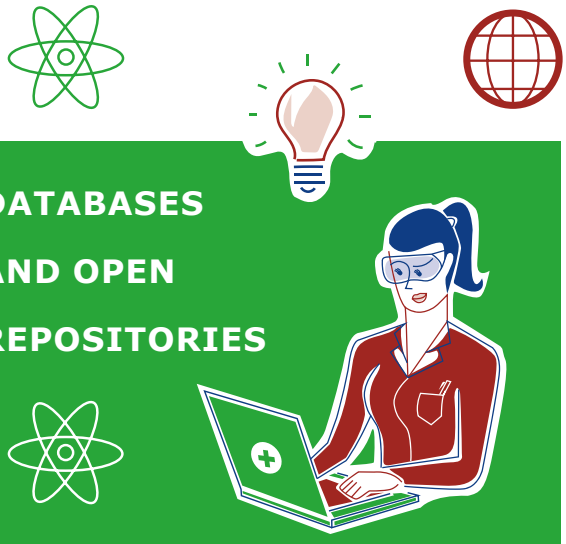

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