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Implementation of the web-based calculator estimating odds ratio of severe COVID-19 for unvaccinated individuals in a country with high coronavirus-related death toll

To the Editor,

Despite one of the world's highest coronavirus-related death rates per capita, only 59% of Polish citizens decided to receive COVID-19 vaccine.[1] Such hesitancy toward vaccination has often been associated with a perception that the risk of being severely infected affects only very narrow group of individuals with certain risk factors and comorbidities.[2] Thus, educational efforts aimed at increasing the community knowledge on actual prevalence and impact of personal risk factors for severe COVID-19 are still warranted.[3] On the contrary, however, quantitative estimation of relative contributions of different host-related risk factors including comorbidities to the severe COVID-19 has still remained elusive.[4] Therefore, here we attempted not only to assess but also rather quantify to which extent well-known phenotypic and comorbid factors impact on the clinical severity of COVID-19.

To this end, we jointly analyzed detailed clinical data from 1186 unvaccinated COVID-19 patients from over a dozen of infectious diseases units and intensive care units located across Poland (Figure S1). The dataset collected directly by physicians contained information about age, sex, height, weight, detailed clinical history, and including chronic comorbidities (hypertension, ischemic heart disease, heart failure, cancer, asthma, chronic obstructive pulmonary disease, autoimmune disease, thromboembolism, and diabetes) (Appendix S1). The severity of COVID-19 was determined for each participant based on the objective parameters including fever, oxygen saturation, arterial gas blood analysis, chest X-ray or computed tomography results, invasive ventilation, and death (Table S1).

We wished to analyze which of the following features: age, sex, body mass index (BMI), or comorbidities can serve the best as a predictor of the severe disease course. For this, we compared logistic regression models considering the abovementioned features and, in order to quantify which feature is the most important for the model, we computed area under the receiver operating curve (AUROC) values of models using one or more of these variables (Figure 1D). Interestingly, we found that the model using jointly all three variables: age, male sex, and BMI had the highest AUROC value (0.730), which was significantly higher than any model using only one variable (AUROC of 0.698 for age, 0.585 for male sex, and 0.574 for

BMI; all *p* values < .0002) (Figure 1D). Quite surprisingly, however, we found that after adjusting for all other predictors, inclusion of chronic comorbidities (at their stable phase) has not improved the accuracy of our model predicting the probability of severe COVID-19 (AUROC 0.730 for age, sex, BMI vs. AUROC 0.724 for age, sex, BMI, and comorbidities; *p* = .917) (Figure 1E and Table S2). The lack of significance of comorbidities in logistic regression model was largely due to the strong correlation of comorbidities with age (Figure S2).[5] It has to be emphasized, however, that our notion regarding comorbidities referred only to the fact of diagnosis of certain comorbidity but not to its current clinical status.

Next, having quantified the relative contribution of age, sex, and BMI for prediction of disease severity, we designed user-friendly odds ratio calculator based on our model and developed an online application providing individual quantitative assessment of odds ratio of development of severe COVID-19. Moreover, to better illustrate to both public opinion and individual users the significance of common determinants in predisposing to severe course of COVID-19, we have created intuitive heatmaps presenting the odds ratio values for individuals of different age, sex, and BMI (Figure 1F).

The application with odds ratio calculator for severe COVID-19 was implemented on February 3, 2022, on the pacjent.gov.pl website to boost the nationwide educational campaign aimed at increasing awareness of the risks related to COVID-19, mainly for those citizens who remained hesitant to the vaccination against COVID-19 (https://pacjent.gov.pl/check-your-risk-severe-covid-19).[6] The pacjent.gov.pl website hosts the Patient Online Account that serves as an online health card for Polish citizens. Within the first week, the application has attracted two hundred thousand users and it has still been used by hundreds of new users daily.

Altogether, our data shed new light on relationships between host-related phenotypic and comorbid risk factors for severe COVID-19. Finally, we demonstrate here an unprecedented in Eastern Europe example of task-specific intense ad hoc collaboration of clinicians and bioinformaticians resulting in creating a patient-oriented digital resource that has successfully been adopted by the public healthcare system. Possibly, given the changing pattern of COVID-19 pandemic, we will be more in need of such personalized tools allowing

(A) kr = 50 test-ROC's and their vertical mean, feature: Age

(B) kr = 50 test-ROC's and their vertical mean, feature: Sex

(C) kr = 50 test-ROC's and their vertical mean, feature: BMI

(D) kr = 50 test-ROC's and their vertical mean, features: Age, Sex, BMI

(E) kr = 50 test-ROC's and their vertical mean, features: Age, Sex, BMI, Comorbidities
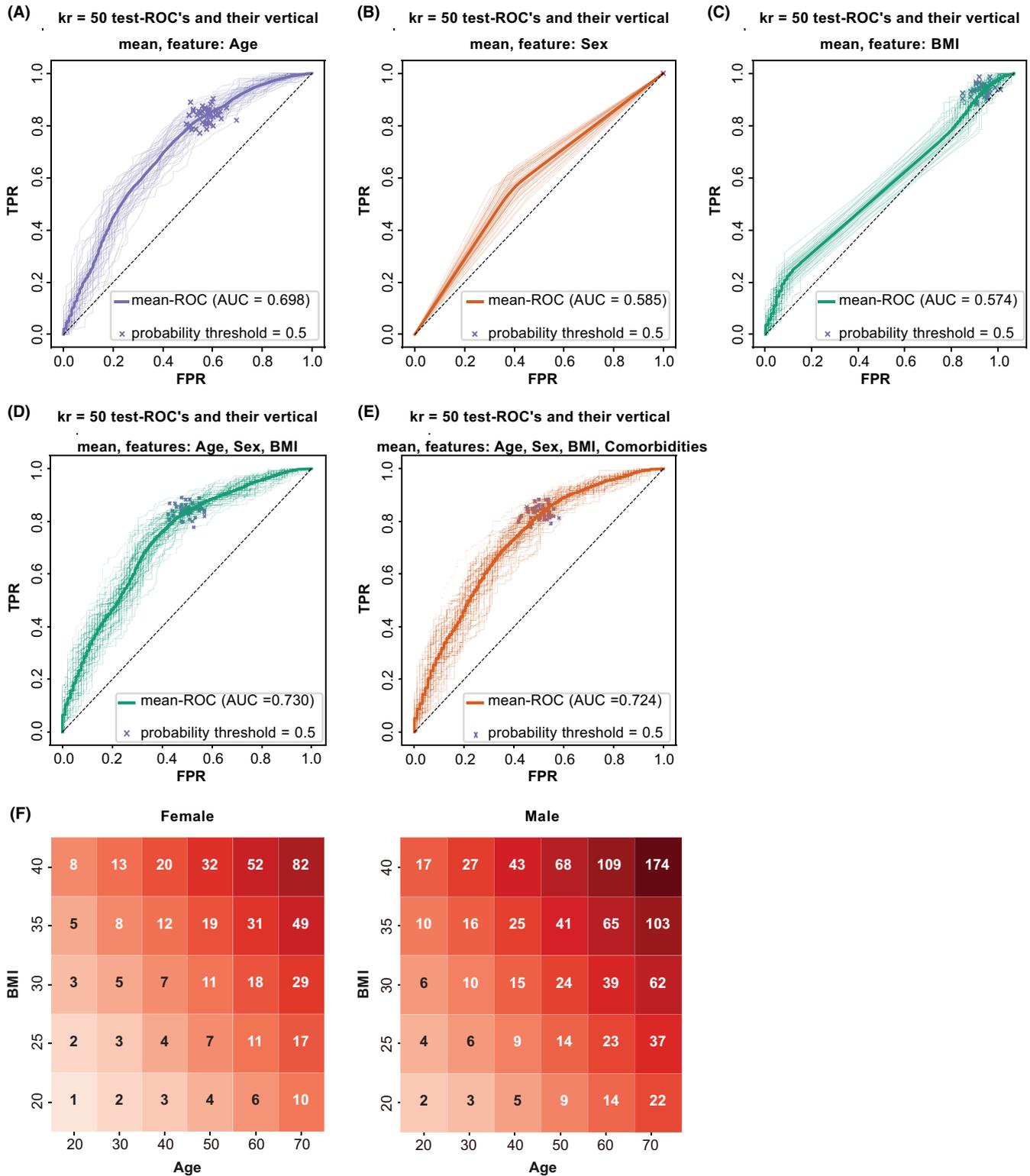
(F)

FIGURE 1 (A–E) Comparison of AUROCs of models with one or more variables. Five logistic regressions were considered with the use of different combinations of variables: A—Age; B—Sex; C—BMI; D—Age, sex, and BMI jointly; E—Age, sex, BMI, and comorbidities jointly. For each ROC (receiver operating characteristic), its area under the curve (AUC) was computed, and the mean of 50 ROC AUC was recorded. Additionally, a mean-ROC curve was constructed by averaging TPR's (true positive rate [TP/P]) for each FPR (false positive rate [FP/N]). (F) Odds ratio calculations of development of severe COVID-19. Sample results were generated using an online odds ratio calculator developed based on our model (https://pacjent.gov.pl/check-your-risk-severe-covid-19). Heatmaps presenting the values of odds ratio for developing severe course of COVID-19 in man and woman based on age, sex, body mass index (BMI). All numbers refer to the individual with the lowest odds (the baseline value of 1)—a 20-year-old woman with BMI of $20\,\mathrm{kg/m^2}$

for selective identification of individuals at risk that should be surrounded by a special care and/or subject to novel anti-viral therapies.

CONFLICT OF INTEREST

All authors from Poland report a grant from Polish Medical Research Agency (ABM) during the conduct of the study (No 2020/ABM/COVID19/0001); JBog and AKru report personal fees from IMAGENE.ME SA outside the submitted work; AJ-S reports personal fees from IMAGENE.ME SA outside the submitted work; JB reports personal fees and other support from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach and other support from KYomed INNOV outside the submitted work; AE and MM received grants from the National Science Centre and the National Research and Development Centre; TFK and MM are the members of the Council of the Medical Research Agency with no right to decide on grant applications and they received no remuneration for the work done in this study; MS received research grant from the Swiss National Science Foundation and from the GSK outside the submitted work; GF is the employee of the National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services; MM reports support from European Commission Horizon 2020 Programme and lecture fees from Berlin-Chemie/Menarini, Astra Zeneca, Novartis, Chiesi, GlaxoSmithKline, Takeda, Teva, Lek-AM outside the submitted work. Other authors declared no conflict of interest within the scope of this work.

PATENT APPLICATIONS

The application for intellectual property protection concerning the creation of the on-line calculator was submitted to the Patent Office of the Republic of Poland under the number P.440399.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.