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Original Scientific Paper

FACTORS ASSOCIATED WITH COVID-19 RELATED DEATH IN 2020 IN CROATIA: A NATIONWIDE OBSERVATIONAL COHORT STUDY

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SUMMARY – The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has had a global effect on mortality. Many attempts were made to identify those at the highest risk of death if infected with SARS-CoV-2, yet the relative importance and global generalizability of individual risk factors remain unclear. At the Croatian Institute of Public Health, electronic health data from multiple databases were combined to examine factors associated with COVID-19 related death. Data on 212 615 patients confir med to have COVID-19 by a positive RT-PCR in 2020 were pseudonymously linked to hospital records and 16 150 hospitalized patients were identified. Apart from older age and male sex, major factors associated with an increased rate of mortality among patients hospitalized with COVID-19 were cardiovascular diseases (adjusted HR: 1.20; 95% CI 1.12-1.28); diabetes (adjusted HR: 1.17; 95% CI 1.09-1.25); and chronic lower respiratory diseases (adjusted HR: 1.10; 95% CI 1.02-1.18). This Croatian study used primary care and hospital data to establish factors associated with COVID-19 related death among patients hospitalized with COVID-19. The results of this study provide rigorous evaluation of the previously defined risk factors and offer guidance for further studies that will create prognostic models based on empirical data from 2020.

Key words: Epidemiology; Health policy; SARS-CoV-2; Virus diseases

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a global effect on mortality. As of February 28, 2021 (date of the latest data availability in this study), 2 520 653 deaths have been reported globally, of which 861 906 were in the World Health Organization (WHO) European Region. The global case fatality rate was 2%, ranging from 0% to 28% in specific countries. By the same day in Croatia, there had been 5 526 COVID-19 related deaths with the same case fatality rate as the global one, 2%[1].

Age, sex and underlying comorbidities have been well established as risk factors for severe COVID-19 outcomes and death[2-4]. On a broader scale, even inter-country variation in COVID-19 case fatality rates can be partially explained by differences in the country-level incidence rates of certain comorbidities and

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socioeconomic factors[5]. Yet, due to a high heterogeneity of study designs and relatively low sample sizes, the relative importance of various underlying conditions is still unclear.

According to the Centers for Disease Control and Prevention, the medical conditions that increase a person's risk of severe illness from COVID-19 are cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus type 1, diabetes mellitus type 2, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), smoking (current and former), obesity, pregnancy and recent pregnancy, with severe illness defined here as hospitalization, admission to the intensive care unit (ICU), intubation or mechanical ventilation, or death[6]. Croatian Society for Infectious Diseases of the Croatian Medical Association assessed the following conditions as risk factors for severe forms of COVID-19: age over 60, diabetes, arterial hypertension, other cardiovascular diseases, chronic lung disease, chronic kidney disease, malignancy, immunodeficiency, and obesity[7], but there have thus far been no empirical studies on the risk factors for COVID-19 related death in Croatia. Results of a study aiming to determine the prevalence of somatic comorbidities in COVID-19 patients in Croatia in the first pandemic wave using data from national public health databases showed that patients who died had a significantly higher prevalence of all investigated comorbidities (diabetes, hypertension, ischemic heart disease, cerebrovascular diseases, cardiomyopathy, diseases of the circulatory system excluding hypertension, chronic lower respiratory diseases, other chronic obstructive pulmonary disease, cancer, and chronic kidney disease) than patients who survived[8]. One small retrospective study on critically ill patients hospitalized in a Croatian ICU has been published showing that lethal outcome was most common in men older than 65 with arterial hypertension, diabetes, and coronary heart disease[9]. While findings from other countries such as China, USA, Belgium, and England[4,10-12] can be of use, their validity in Croatia should be checked due to significant differences in clinical, socioeconomic and demographic characteristics of the populations and due to differences in the organization of health care systems and hospital utilization patterns.

Primary care electronic health records and electronic hospital records in Croatia are rarely combined for research purposes on a population scale, but understanding this novel pandemic requires such a broad population level integrated studies. Therefore, in this study we set out to use and integrate available electronic health records to investigate the population risk factors associated with in-hospital COVID-19 related deaths in Croatia.

Our objective was to determine the factors associated with COVID-19 related death among the entire cohort of hospitalized COVID-19 cases in 2020 in Croatia.

Subjects and Methods

Study design

We conducted a cohort study using national primary care electronic health record data from the Central Health Information System of the Republic of Croatia (*Centralni zdravstveni informacijski sustav Republike Hrvatske*, CEZIH) linked to electronic hospital records from the National Public Health Information System of Croatia (*Nacionalni javnozdravstveni informacijski sustav*, NAJS). The cohort study included all hospitalized patients confirmed to have COVID-19 by a positive reverse transcription polymerase chain reaction (RT-PCR) test in 2020. Data extraction was carried out at the beginning of March 2021 to ensure that hospitalization data on all cases were gathered until at least January 31, 2021, i.e., that all cases were followed for at least one month after receiving a positive RT-PCR test. This cohort study examined mortality risk only among the population infected with SARS-CoV-2 that were hospitalized and not among the entire infected population.

Our study population consisted of all patients (males and females, children and adults) that were registered as having been hospitalized while being an active COVID-19 case and/or were registered as having been hospitalized with COVID-19 as a primary discharge diagnosis in NAJS. We looked at primary health care records of these patients in the 2018-2021 period and discharge diagnoses of their recorded hospitalizations in the study period. Patients were followed until either their death date or date of data extraction, March 9,

2021, whichever came first. No randomization or blinding was undertaken. Outcome data were gathered as part of standard hospital routine and study investigators had no involvement in outcome assessment.

Data sources

Data from clinical laboratories and primary health care providers were collected using CEZIH. All COVID-19 test results were obtained from clinical laboratories and pertained to all individuals whose nasopharyngeal swab samples were tested for SARS-CoV-2 in Croatia from January 30, 2020 to December 31, 2020. Furthermore, data pertaining to all COVID-19 patient visits to their primary health care providers in the period from January 1, 2018 until January 31, 2021 were collected. All diagnoses recorded during reported visits were analyzed to determine comorbidities of COVID-19 patients. NAJS, administered by the Croatian Institute of Public Health (CIPH), was used as the source of data pertaining to hospital patients. Data were obtained from inpatient statistical forms, completed whenever a patient was discharged from a hospital. For the purpose of this study, all available inpatient statistical forms contained in the NAJS system pertaining information on COVID-19 patients in the period from January 1, 2018 to March 9, 2021 (extraction date) were analyzed. The variables of interest were the main diagnosis at discharge and other diagnoses recorded during hospital treatment.

CEZIH data were submitted for analysis to CIPH by the Croatian Health Insurance Fund (CHIF). Data were linked and analyzed in CIPH. Data on COVID-19 patients and their comorbidities recorded in CEZIH and NAJS systems, as well as all other data relevant to the study were extracted using SQL Server Management Studio 18 software (Microsoft, Redmond, WA, USA) and combined to a single database. Data were extracted on March 9, 2021 in order to give hospitals enough time to report the required data. All patient records were pseudonymized and linked using a unique patient ID. Study investigators had no access to patient information before pseudonymization.

Since Croatia has a universal health care system, data from CHIF are a valid source of information for the entire population. NAJS is an organized system of information services by CIPH, shared with partner institutions. NAJS contains multiple public health registries and databases; for the purpose of this study, we obtained information from databases in the hospital domain, i.e., the hospitalization, rehabilitation, and day-care hospital treatment database[13]. All health institutions that provide stationary health care in Croatia are obliged to complete and submit inpatient statistical forms to the NAJS system using the provided data channels. CEZIH is owned by the Ministry of Health of the Republic of Croatia and operated by CHIF[14]. It is an integrated information system that connects and controls all peripheral information systems in primary care doctor offices.

Variables

There was one primary outcome, i.e., in-hospital death among all hospitalized patients confirmed to have COVID-19 by a positive RT-PCR test between February 24, 2020 and December 31, 2020.

Categorical (binary) indicators of comorbidities deemed relevant according to the Croatian Society for Infectious Diseases of the Croatian Medical Association and present in the dataset were chosen as covariates as follows: diabetes, primary hypertension, other cardiovascular diseases, chronic lung disease, chronic kidney disease, malignant neoplasms, immunodeficiency, obesity, along with sex, age, and the socioeconomic development level of patient municipalities.

Diabetes mellitus was recorded if the patient was registered in the Croatian National Diabetes Registry (CroDiab). All general practitioners and hospital physicians treating persons with diabetes mellitus must mandatorily register their patients in the CroDiab registry since 2004[15].

All other studied comorbidities were recorded if at least one respective entry was present in the NAJS hospitalization database (as the main or other discharge diagnoses) or the CEZIH primary care database (as any diagnosis, i.e., main, additional, or recipe diagnosis). For primary hypertension, only diagnoses under the International Classification of Diseases 10th Revision (ICD-10) code I10 were considered. Other cardiovascular diseases were for the purpose of this study defined as all diseases of the circulatory system (I00-I99) apart from I10. Chronic lung disease was for the purpose of this study observed somewhat wider, so as to include all chronic lower respiratory diseases (J40-J47). Chronic kidney disease was for

the purpose of this study defined as glomerular diseases, renal tubulo-interstitial diseases, renal failure, urolithiasis, and other disorders of kidney and ureter (N00-N29). For malignant neoplasms, all diagnoses under the ICD-10 codes C00-C97 were considered. Immunodeficiency was defined as certain disorders involving the immune system (D80-D89) or the human immunodeficiency virus (HIV) disease (B20-B24). Since obesity (E65-E66) is underdiagnosed in the Croatian health care system (e.g., in 2019, only 8857 cases were diagnosed in the adult population by the General Medical Service[16] while survey data suggest that 18% of the adult population have obesity[17]), diagnosis data on obesity were deemed unreliable. Data on weight and height recorded in primary care preventive panels were considered for calculation of the body mass index (BMI), but since preventive panels are not mandatory in Croatia, we had complete BMI data only for 43% of the patients. Due to the very high level of missing data and in order to preserve the majority of the dataset, obesity was not included as a covariate in the model, and subsequently not investigated as a risk factor.

Age was trichotomized into three binary variables, each indicating whether the participants were younger than 55 (the reference group), aged between 55 and 64, or older than 64. As a measure of the socioeconomic development level of patient municipalities, we used the official classification by the Ministry of Regional Development and EU Funds. The Ministry divides all municipalities in Croatia into octiles based on the value of a composite Human Development Index (HDI), with the first octile being the one with the lowest index value. HDI is a function of z-score values of the following six socioeconomic indicators: (i) average residents' income *per capita*, (ii) average budget revenue *per capita*, (iii) average unemployment rate, (iv) population change, (v) tertiary education rate, and (vi) aging index[18].

The length of hospital stay was calculated as the interval between hospital admission and hospital discharge or death.

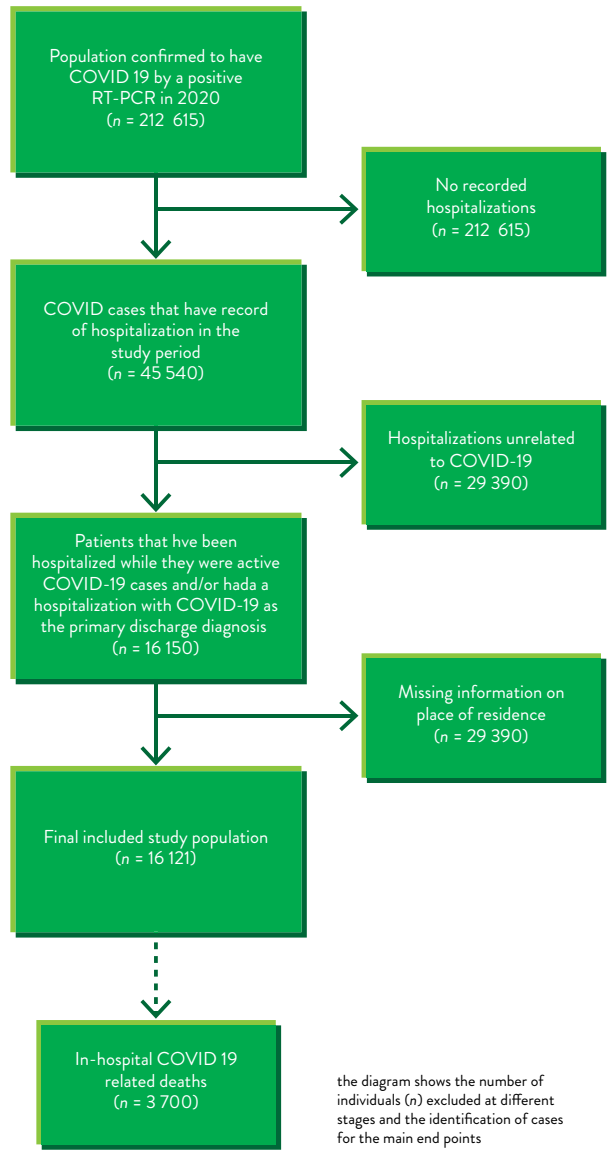

Fig. 1. Flow diagram of the study cohort.

Statistical methods

To estimate the risk of death and its association with the above-discussed covariates, we used a multivariable mixed-effects Cox proportional hazards model. We added individual hospitals as random effects to account for the structure of data and dependence among clustered observations, which can otherwise cause erroneous rejections of null hypotheses and invalidate the interpretation of confidence intervals (CIs) associated with the point estimates[19,20]. We used robust standard errors in the estimation. Observations of patients discharged from the hospital were censored

at the date of discharge (no patients were still hospitalized at the end of data collection). We reported hazard ratios (HRs) for each covariate and the model C index as the measure of fit[21]. A 2-tailed $p<0.05$ was considered statistically significant. R version 4.0 and packages survival and mppa were used for analyses.

Ethics

This study was approved by the Croatian Institute of Public Health Ethics Committee (class: 030-02/21-07/1, Reg.no. 381-15-21-2). The research was performed in accordance with relevant guidelines and regulations. Considering that this study used retrospective pseudonymized data from national electronic health record databases, patient consent for this study was not possible to obtain and was not required by the Croatian Institute of Public Health Ethics Committee.

Results

Subjects

Complete dataset contained information on 212615 people with a positive SARS-CoV-2 test (Fig. 1). A total of 16150 subjects were admitted to a hospital while being an active COVID-19 case and/or were registered as having been hospitalized with COVID-19 as a primary discharge diagnosis between February 24, 2020 (date of first registered COVID-19 case in Croatia) and February 26, 2021.

Data on socioeconomic development due to missing municipality data were missing for 29 (1.8%) observations; after removing those observations, there were 16121 observations remaining in the final dataset (cohort description in Table 1). The dates of admission, death (if death occurred during relevant

Table 1. Cohort description with number of COVID-19 deaths by patient characteristics

Characteristic	Category	Number of individuals (column %)	Number of COVID-19 related deaths (% within stratum)
Total		16121 (100.0)	3700 (23.0)
Age (yrs)	<55	3511 (21.8)	151 (4.3)
	55-64	3090 (19.2)	411 (13.3)
	>64	9520 (59.0)	3138 (33.0)
Sex	Female	7237 (44.9)	1546 (21.4)
	Male	8884 (55.1)	2154 (24.2)
Hypertension		11703 (72.6)	3145 (26.9)
Other cardiovascular diseases		5831 (36.2)	1909 (32.7)
Immunodeficiency		304 (1.9)	58 (19.1)
Malignant neoplasms		2863 (17.8)	842 (29.4)
Diabetes		4303 (26.7)	1313 (30.5)
Chronic kidney disease		139 (0.9)	36 (25.9)
Chronic lower respiratory diseases		3246 (20.1)	900 (27.7)
Developmental index (octiles)	1	670 (4.2)	166 (24.8)
	2	903 (5.6)	194 (21.5)
	3	1162 (7.2)	260 (22.4)
	4	1787 (11.1)	383 (21.4)
	5	1402 (8.7)	300 (21.4)
	6	2085 (12.9)	460 (22.1)
	7	1909 (11.8)	449 (23.5)
	8	6203 (38.5)	1488 (24.0)

hospitalization), or discharge were present for all the remaining observations. The patients included were hospitalized in 74 hospitals across Croatia. In-hospital COVID-19 related deaths were recorded for 3700 (23.0%) of the 16121 subjects.

Main results

The estimated adjusted HRs for all the covariates – the exponentiated fixed effect coefficients from the multivariable mixed-effects Cox proportional hazard model are presented in Table 2, along with the associated 95% CIs. The adjusted estimates and CIs are also graphically presented in Figure 2. The model C index was 0.7.

Table 2. Hazard ratios and 95% confidence intervals for COVID-19-related death

Covariate	Hazard ratio	p value	95% Confidence interval
Age >64 years	4.777	<0.001	4.02-5.676
Age 55-64 years	2.155	<0.001	1.783-2.604
Male	1.256	<0.001	1.176-1.343
Other cardiovascular diseases	1.197	<0.001	1.119-1.281
Diabetes	1.168	<0.001	1.09-1.252
Chronic lower respiratory diseases	1.099	0.015	1.019-1.185
Malignant neoplasms	1.044	0.275	0.966-1.129
Developmental index (octiles)	1.015	0.108	0.997-1.034
Hypertension	0.932	0.159	0.845-1.028
Chronic kidney disease	0.863	0.381	0.621-1.2
Immunodeficiency	0.856	0.244	0.66-1.112

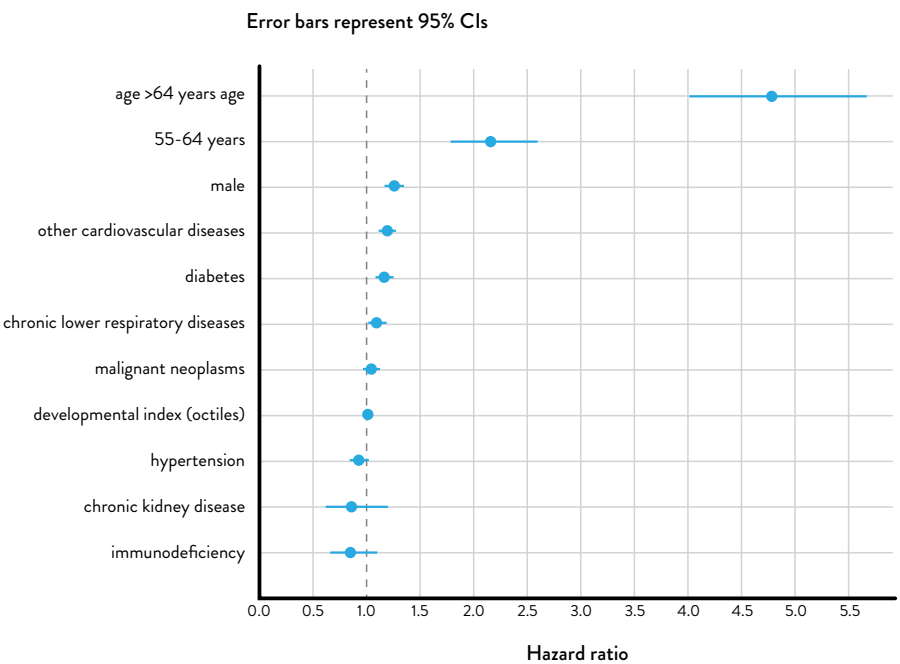

Fig. 2. Hazard ratios for all covariates among patients hospitalized with COVID-19; outcome: death.

CI = confidence interval

Discussion

Key results

Apart from the two higher age groups and male sex, the HR estimates significantly above 1 were those for other cardiovascular diseases (adjusted HR: 1.20; 95% CI 1.12 to 1.28; p<0.001); diabetes (adjusted HR: 1.17; 95% CI 1.09 to 1.25; p<0.001); and chronic lower respiratory diseases (adjusted HR: 1.10; 95% CI 1.02 to 1.18; p<0.001). During the COVID-19 pandemic in Croatia, these appear to be the major comorbidities associated with an increased rate of mortality among patients hospitalized with COVID-19.

It has been established in previous studies that persons aged ≥65 have much higher COVID-19 mortality rates compared to younger persons[22], and that, even though the number of deaths varies largely among countries, the age distribution in COVID-19 mortality is rather robust, which cannot be explained by variation of susceptibility by age[23].

A global COVID-19 meta-analysis has identified male sex as a risk factor for death[24]. The higher COVID-19 mortality in males can be explained by sex differences in immune response and cardiovascular comorbidities[25], angiotensin-converting enzyme 2 (ACE2) activity[26], or testosterone levels[27].

Previous studies have shown that diabetes has been associated with increased COVID-19 related mortality, which was associated with cardiovascular and renal complications of diabetes, glycemic control, and BMI[28]. Further studies are still needed to assess whether the association of diabetes with increased COVID-19 related mortality is independent or can be explained by other factors such as appropriate glycemic regulation prior to infection with COVID-19[29].

Pre-existing respiratory diseases have been identified as an important predictor of mortality in COVID-19 patients in some previous studies[30,31] but recent studies have shown that the extent of this increased risk, particularly in people with asthma, might be lower than originally thought[32], which is in line with the results of this study.

Many studies have shown that various cardiovascular diseases are significantly associated with mortality in COVID-19 patients, with acute cardiac injury bearing the highest odds ratio for mortality[33]. When it comes to hypertension specifically, previous studies have shown mixed results. While some evidence showed that hypertension significantly increased the risk of fatality of SARS-CoV-2 infection[34], an inverse association of hypertension and mortality was observed in other studies where similar comorbidities as here were included in the model[4] and where blood pressure control before COVID-19 diagnosis was examined[35]. Also, several studies, just like this one, found that hypertension was not an independent predictor of COVID-19 mortality when controlling for other comorbidities[36,37], which reinforces the need of further specific research of hypertension as a possible independent risk factor for COVID-19 mortality.

Evidence for immunodeficiency as a risk factor for COVID-19 related death has so far not been conclusive[38,39], and this study further substantiates this. It is likely that certain types of immunodeficiency have a greater effect on COVID-19 mortality than others, which should be further investigated in new studies. For now, classifying the diverse group of immunodeficiencies as a general risk factor for COVID-19 related mortality does not seem to be justified.

Perhaps surprisingly in the light of previous research on renal diseases[40] and cancer[41] as risk factors for mortality with COVID-19, in this study the hazard rate for those with the conditions was on average not higher than for those without them. As far as renal diseases are concerned, this could be due to the somewhat broader definition of these diseases used in this study as the severity of renal disease was not precisely staged in most of our primary care data set in comparison to other studies that only looked at renal failure and conditions requiring dialysis. Concerning cancer, there have been reports that the overall COVID-19 attributable mortality in cancer patients is affected by age, gender, comorbidity, and specific cancer types[42,43], which may be the reason that, in this type of study, no independent association between cancer and increased mortality has been observed, as in some other population-based studies controlled for age and sex[44].

The uncertainty associated with the estimated HR of the HDI consisting of 6 socioeconomic indicators was likewise inconclusive. In other high income countries, a strong association has been found between deprivation and COVID-19 related death[4,45], yet here we found no significant association. This could be because some of the socioeconomic variations may have been

captured by the random effects of the model through differences in hazard rates associated with particular hospitals.

Strengths and limitations

The greatest strengths of this study are its size and scale. By using pseudonymized national electronic health records, we were able to assess risks for in-hospital COVID-19 related death for the entire Croatian population, while still maintaining patient privacy. We combined data from multiple electronic health databases to gather information from both the primary health care system and hospital records, which allowed us to ascertain the presence of known comorbidities with greater confidence.

The study is not without limitations, though. Since this observational study used a dataset of all patients in Croatia with positive SARS-CoV-2 test results that were hospitalized, this makes it susceptible to collider bias. Frailty, i.e., greater susceptibility to adverse outcomes, is both a predictor for hospitalization, as well as for death from COVID-19[46]. Also, our findings reflect only an individual's risk of dying once infected with COVID-19 and hospitalized. They do not reflect an individual's risk of infection with COVID-19 or hospitalization due to COVID-19.

In our population definition, we included only patients confirmed to have COVID-19 by a positive RT-PCR test. It should be noted that patients with positive rapid antigen tests that were hospitalized for COVID-19 related reasons but did not have a positive RT-PCR test were not included in this study, which may have resulted in some patients being incorrectly excluded from the observed population. Also, even though Croatia has a universal health care system, it is possible that some persons have no insurance and are thus not included in this study, which may be the case if they are foreign citizens or they have not applied for insurance on any grounds.

Primary care records were incomplete for data on obesity. Since obesity is underdiagnosed and preventive panels with information on weight and height are not regularly filled out for all patients, we had no reliable information on obesity or BMI for all the patients. Obesity is a well-recognized risk factor for COVID-19 related mortality[3,4,47,48] and here presents an unmeasured covariate that might have influenced model fit or hazard proportionality. The inability of obtaining valid population-level data on BMI/obesity for this study should serve as an incentive for establishing a regular population-level surveillance system on obesity in Croatia.

We present a mutually 'adjusted model' that is not suitable for causal interpretation. Interpreting the estimates as causal effects should be taken with caution since the reported estimates only estimate the association between various characteristics and death of patients hospitalized with COVID-19, and the results should be interpreted accordingly. The meaning of the term risk factor, as used in this study, is a predictor, without attention to cause.

Furthermore, the data exhibited statistically significant violations of the proportional hazard assumption of the Cox model for the age group variables, sex, hypertension, other cardiovascular diseases, and diabetes (extended data in Fig. 1). However, visual inspection of the Schoenfeld residuals revealed no substantial departure from the assumption about a lack of time dependence[49]. With a considerable sample size, even minor departures are likely to be statistically significant, while some time dependency may even be expected[50].

While the interpretation of the overall estimated HRs should in the light of this possible violation be as a weighted average of the time-varying HRs for each variable, the estimated CIs can be interpreted straightforwardly in the light of the conservative usage of robust standard errors and of the mixed-effects version of the model to account for correlations between clustered observations.

Implications for policy and further research

This study illustrates the potential of linked administrative data to provide timely insights into COVID-19. It reveals much about the characteristics associated with death from COVID-19 in Croatia and should be used as a base for redefining Croatian criteria for being at a high risk of developing severe forms of COVID-19.

While these types of national studies have limited external validity due to differing sociodemographic and clinical characteristics of populations worldwide and differing national health systems, these results confirm findings from previous studies that the risk

of death from COVID-19 is higher in males, older people, and people with certain pre-existing conditions (cardiovascular diseases, diabetes, chronic lower respiratory diseases), which contributes to determining the generalizability of these risk factors globally. Because this study only looked at hospitalized patients, we can reasonably assume that the established associations are not due to greater disease susceptibility or severity, but the nature of this study cannot provide any insight into why people with these characteristics experienced higher risks. These findings, along with those from previous similar studies, should be used to inform further studies with causal inference methods that would give such explanations and help clarify the generalizability of these associations.

Interestingly, other pre-existing conditions that have been established as significant risk factors elsewhere (cancer, renal diseases) were not found to have higher hazard rates here, which definitely warrants further research. The finding that poor local socioeconomic development is not a risk factor for death from COVID-19 in Croatia, unlike some other countries, might also be interpreted as an indicator of the importance of local conditions for determining the external validity of established risk factors for COVID-19 mortality.

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Sažetak

ČIMBENICI UDRUŽENI SA SMRTNIM SLUČAJEVIMA POVEZANIM S COVID-19 U 2020. GODINI U HRVATSKOJ: NACIONALNA OPSERVACIJSKA KOHORTNA STUDIJA

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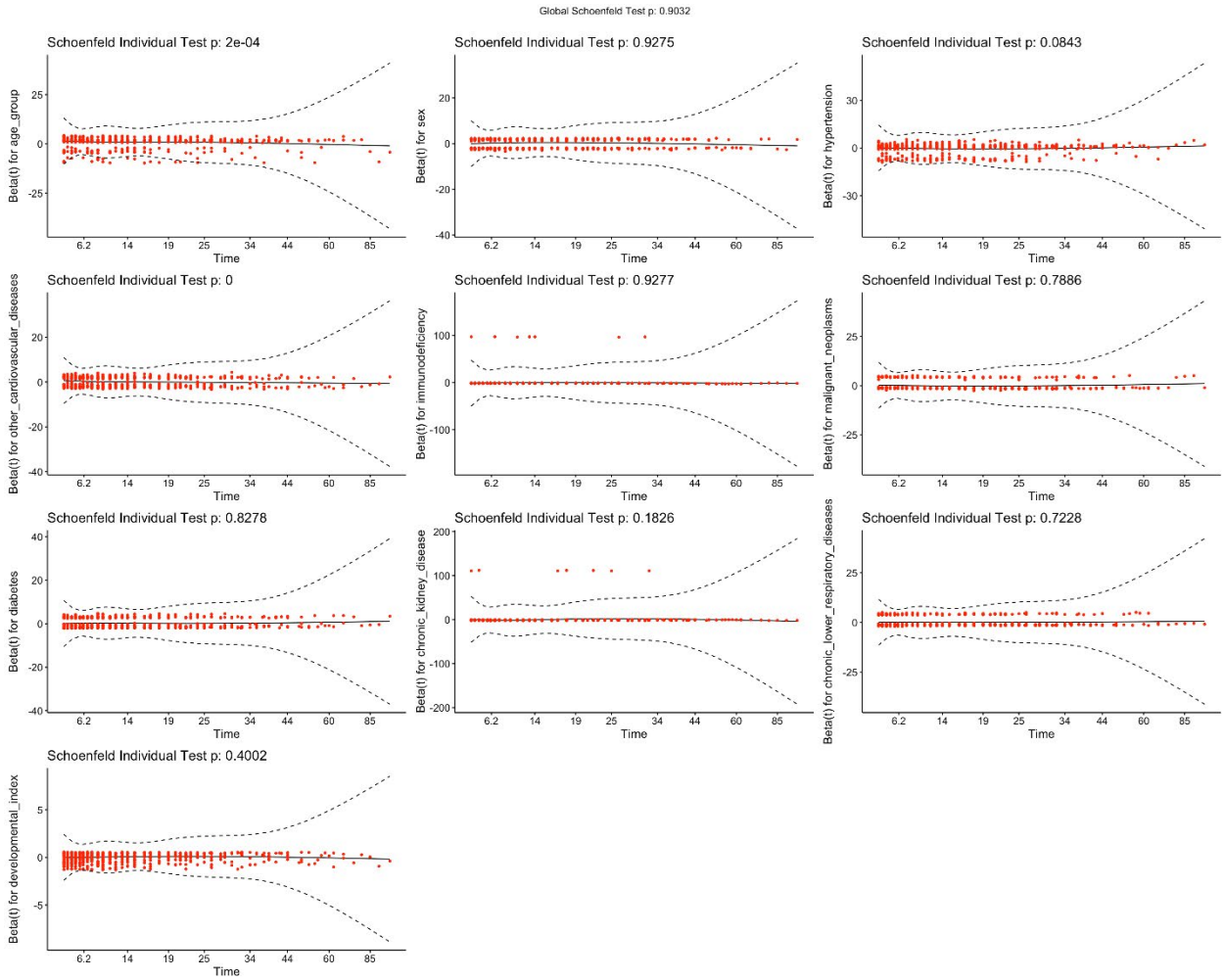
Koronavirusna bolest 2019 (COVID-19) uzrokovana virusom SARS-CoV-2 utjecala je na globalnu smrtnost. Bilo je mnogo pokušaja identifikacije onih koji su u najvećem riziku od smrti uslijed zaraze virusom SARS-CoV-2, ali je relativna važnost i mogućnost globalne generalizacije pojedinih rizičnih čimbenika i dalje nejasna. Pri Hrvatskom zavodu za javno zdravstvo spojeni su elektronički zdravstveni podaci iz više baza podataka kako bi se istražili čimbenici povezani sa smrću od COVID-19. Podaci o 212.615 bolesnika koji su imali COVID-19 potvrđen pozitivnim RT-PCR u 2020. godini su putem pseudonima povezani s bolničkim podacima te je identificirano 16.150 hospitaliziranih bolesnika. Uz stariju dob i muški spol glavni čimbenici povezani s povišenom stopom smrtnosti među hospitaliziranim bolesnicima s COVID-19 bile su kardiovaskularne bolesti (prilagođeni HR: 1,20; 95% CI 1,12-1,28), šećerna bolest (prilagođeni HR: 1,17; 95% CI 1,09-1,25) i kronične bolesti donjeg dišnog sustava (prilagođeni HR:1,10; 95% CI 1,02-1,18). U ovoj hrvatskoj studiji rabili su se podaci iz primarne zdravstvene zaštite te iz bolnica kako bi se utvrdili čimbenici povezani sa smrću od COVID-19 među bolesnicima hospitaliziranima zbog COVID-19. Rezultati ove studije predstavljaju rigoroznu evaluaciju prethodno definiranih rizičnih čimbenika i nude smjernice za buduća istraživanja u kojima bi se izradili prognostički modeli na osnovi empirijskih podataka iz 2020. godine.

Ključne riječi: *Epidemiologija; Zdravstvena politika; SARS-CoV-2; Virusne bolesti*



Extended data Fig. 1. Diagnostic plots relating Schoenfeld residuals with time (measured in days from admission) for each age group, sex, hypertension, other cardiovascular diseases, immunodeficiency, malignant neoplasms, diabetes, chronic kidney disease, chronic lower respiratory diseases and development index.