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# COMORBID CONDITIONS IN A COHORT OF INPATIENTS WITH SARS-COV-2 AND THEIR ASSOCIATION WITH IN-HOSPITAL MORTALITY DURING THE EARLY PHASES OF THE PANDEMIC

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## ABSTRACT

**Introduction**: Studies determined that age and associated comorbidities are associated with worse outcomes for COVID-19 patients. The aim of the present study is to examine previous electronic health records of SARS-CoV-2 patients to identify which chronic conditions are associated with in-hospital mortality in a nationally representative sample.

**Materials and Methods**: The actual study is a cross-sectional analysis of SARS-CoV-2 infected patients who were treated in repurposed hospitals. The study includes a cohort of patients treated from 06-11-2020 to 15-03-2021 for COVID-19 associated pneumonia. To examine the presence of comorbidities, electronic health records were examined and analyzed.

**Results**: A total of 1486 in-patients were treated in the specified period, out of which 1237 met the criteria for case. The median age of the sample was 65 years. The overall in-hospital mortality in the sample was 25.5%, while the median length of stay was 11 days. From whole sample, 16.0% of the patients did not have established diagnoses in their electronic records, while the most prevalent coexisting condition was arterial hypertension (62.7%), followed by diabetes mellitus (27.3%). The factors of age, male gender, and the number of diagnoses showed a statistically significant increase in odds ratio (OR) for in-hospital mortality. The presence of chronic kidney injury was associated with the highest increase of OR (by 3.37) for in-hospital mortality in our sample.

**Conclusion**: The study reaffirms the findings that age, male gender, and the presence of comorbidities are associated with in-hospital mortality in COVID-19 treated and unvaccinated patients. Our study suggests that chronic kidney injury showed strongest association with the outcome, when adjusted for age, gender, and coexisting comorbidities.

**Keywords**: sars-cov-2; pandemic; non-communicable diseases; chronic diseases; comorbidities; in-hospital mortality

## INTRODUCTION

The spread of the novel SARS-CoV-2 created a global challenge for health systems [1], leading to an unprecedented rise in in-hospital mortality, excess mortality and patients with long term sequelae [2], [3]. It has been established that age, gender and the comorbid profile [4]–[7] are strongly predictive of worse outcomes when patients are infected with SARS CoV-2. Additionally, the peaks of the pandemic caused such pressure that other factors became important as well, such as availability of hospital beds, population density and age structure of the population [8], [9]. Its comparison to viruses with a similar mode of transmission and manifestations, such as the influenza virus, revealed worse hospital outcomes in all age groups [10] during the early phases of the pandemic. The presence of comorbidities is a non-specific marker [11] for mortality (both in-hospital and within 30 days), and so far few scales have been used to predict mortality even among patients with COVID-19 illness. For instance, the Charlson Comorbidity Index [12] was subjected to such an analysis, with a reported 16% rise of risk of mortality from COVID-19 for every additional point on that scale [13].

Existing electronic patient data is already used for planning purposes, for customization of treatment and for retrieval of relevant information, more so when patients are unable to describe their medical history. In the case of the RN Macedonia, the electronic health record system (EHRS) "MojTermin" was established in 2012, aiming to capture every interaction of the patients with public health providers, including existing diagnoses and prescriptions. The aim of the present study is to identify which comorbidities can be retrieved from the (EHRS), MojTermin, [14] and are associated with in-hospital mortality. The study also takes into consideration the gender and the age of the patient. Additionally, this study explores whether the number of registered comorbidities can serve as proxy for comorbidity measure to predict in-hospital mortality. Since no similar measurement tool of comorbidity has been validated on a country level, this was approached by accounting for the presence of common chronic comorbidities based on past literature and findings from the preliminary analyses (Supplement 2). On the basis of past findings, it is anticipated that patients older male patients, and patients with a higher count of comorbidities have a substantially higher risk for in-hospital mortality.

## METHODS AND MATERIALS

The present study is a cross-sectional study, using data from all hospitalized patients in 7 teaching hospitals during the second and third wave of SARS-COV-2 in our country. Shortly before the emergence of the second peak, these hospitals were re-purposed for providing care for SARS-COV-2 infected patients, with the limitation of providing ward-care only, without ICU facilities (Supplement 1). The admitted patients were patients with the confirmed presence of SARS-COV-2 either by PCR test [15] from a licensed virological laboratory, by a fast antigen test, or had the clinical presentation of COVID-19 supported by imaging. The resulting cohort consists of patients that were not vaccinated at that time, during which there was a predominance of the wild type and the introduction of the alpha variant (since February 2021). All patients that were hospitalized during the period of 06-11-2020 to 15-03-2021 are included in the analysis. The study was conducted in accordance with the STROBE guidelines [16].

Data on comorbidities were retrieved by physicians, blinded to outcomes, with the following list of comorbidities: presence of arterial hypertension, presence of diabetes mellitus, presence of active malignancy, obesity, chronic cardiological conditions, chronic respiratory conditions, hematological conditions, chronic kidney injury, sequalae from neurological injury, the presence of hypothyroidism, the presence of significant gastrointestinal conditions. Details on the process and the pilot are available in Supplement 2. The local ethics committee approved the study design and allowed for commencement of the study. The choice of specific comorbidities was given based on previous literature reports at the time (Oct-2020); additionally, data on gastrointestinal conditions and hypothyroidism were included, owing to the previous availability of data in MojTermin. The purpose of these additional diagnostic groups which are not related to the outcome is to serve as control for the data collection procedure, with the expectation that the presence of these comorbidities is not statistically significantly associated with in-hospital mortality in our patient group.

## ANALYSIS

Data on the whole sample of patients was summarized by using appropriate measures of central tendency and dispersion (median, IQR or mean value and SD) for continuous and counts and proportions for dichotomized variables and were evaluated graphically. Patients were further divided into equal age categories on basis of quintiles of the data into 4 groups. Analysis was done to compare the deceased patients with the survived patients and comparisons were made by using non-parametric tests. Inter-rater agreement was checked by using the Cohen's kappa. Records on comorbid conditions were calculated as simple sums from all comorbidities and selected comorbidities that attained statistically significant association with mortality and/or are considered as theoretically important. The resulting scale was considered as ordinal variable and was checked for correlation with age and mortality outcomes. Next, binomial logistic regression models with in-hospital mortality as dependent outcomes were created, first with age and gender as predictors, and then with each associated comorbidity, adjusted for age category and gender, while the final model used the final score described previously. Analyses were done in IBM SPSS v.26 [17].

## RESULTS

During the study period there were 1486 hospitalized patients. From all of them, 33 patients withdrew from hospital care and were not included in further analysis. Additionally, 87 patients had negative tests for SARS-CoV-2 on admission, and hence were not included in further analysis. From the remaining 1366 patients, 129 patients were transferred to other hospitals, leaving the final sample to consist of data on 1237 patients (see Fig.1). The median age of the sample was 65 years, and 60.3% of the patients were male, while 832 (67.3%) patients were diagnosed with rt-PCR test. Descriptive characteristics of the cohort are available on Table 1. Cases of mortality were 315, or 25.5% of the sample. From all patients, 198 patients did not have any registered comorbidities in their EHR. From 1237 patients, 320 patients (25.9%) were with single registered comorbidity, while 719 patients (58.1%) had 2 or more comorbid conditions. The most prevalent comorbid condition was arterial hypertension (62.4%), followed by diabetes mellitus (27.3%). Details on the comorbidities in our sample are presented in Table 1 (by gender) and Table 2 (by status).

The group of deceased patients showed substantial differences regarding age, length of stay, presence of arterial hypertension, diabetes mellitus, cardiological, hematological conditions, neurological sequelae, chronic kidney disease, while there was no substantial association with presence of registered chronic respiratory diseases, malign conditions, obesity, thyroid disease, and GI conditions. In the group of deceased patients, there were 15 cases (4.7% of all cases of in-hospital mortality) that did not have any previous registered diagnosis in their EHR. This group of patients had median age of 69 (with IQR – 12), while 11 (73.3%) of them were male.

On the basis of presence of the above-mentioned comorbidities, the score was calculated for each patient as simple sum of diagnoses; the score was binary (either 0 or 1) for each comorbidity and accounted for the presence of 1) arterial hypertension, 2) diabetes mellitus, 3) chronic respiratory conditions, 4) cardiological conditions, 5) chronic kidney disease, 6) hematological conditions and malignancies, 7) other active malignancies and 8) neurological sequelae. Due to the low number of patients with 4 or more diagnoses, these categories were collapsed

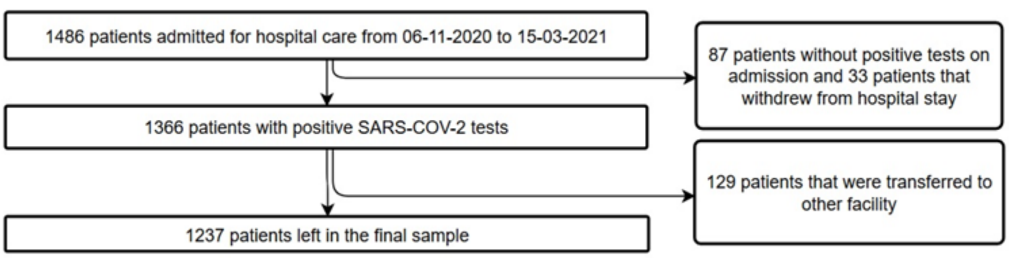


**Figure 1.** *Flowchart of the patient population*

**Table 1.** *Descriptive characteristics for whole sample and by gender (n= 1237)*

| Variable | Total | | Males (746, 60.3%) | | Females (491, 39.7%) | |
|---|---|---|---|---|---|---|
| Age, median, IQR | 65 | 12 | 64 | 18 | 66 | 21 |
| Age category, 16-55 y, count, % | 336 | 27.2% | 217 | 29.1% | 119 | 24.2% |
| 56-65, count, % | 312 | 25.2% | 193 | 25.9% | 119 | 24.2% |
| 66-73, count, % | 291 | 23.5% | 178 | 23.9% | 113 | 23 % |
| 74 or more years, count, % | 298 | 24.1% | 158 | 21.2% | 140 | 28.5% |
| Type of test, rt-PCR, % | 832 | 67.3% | 523 | 70.1% | 309 | 62.9% |
| Rapid antigen test | 405 | 32.7% | 223 | 29.9% | 182 | 37.1% |
| Length of stay, days, median, IQR | 11 | 8 | 11 | 8 | 12 | 8 |
| Arterial hypertension, count, % | 776 | 62.7% | 454 | 58.5% | 322 | 41.5% |
| Diabetes mellitus | 338 | 27.3% | 191 | 56.5% | 147 | 43.5% |
| Malign diseases | 77 | 6.2% | 40 | 51.9% | 37 | 48.1% |
| Chronic respiratory conditions | 156 | 12.6% | 83 | 53.2% | 73 | 46.8% |
| Chronic cardiological conditions | 293 | 23.7% | 174 | 59.3% | 119 | 40.1% |
| Hematological conditions | 74 | 5.9% | 34 | 45.9% | 40 | 54.1% |
| Chronic kidney injury | 114 | 9.2% | 66 | 57.9% | 48 | 42.1% |
| Neurological sequelae | 192 | 15.5% | 118 | 61.4% | 74 | 38.5% |
| Thyroid disease | 90 | 7.3% | 20 | 22.2% | 70 | 77.8% |
| Gastrointestinal conditions | 210 | 16.9% | 126 | 60% | 84 | 40% |
| No comorbidities | 198 | 16.0% | 147 | 74.2% | 51 | 26.8% |
| 1 comorbid condition | 320 | 25.9% | 185 | 57.8% | 135 | 42.2% |
| 2 comorbid conditions | 305 | 24.7% | 183 | 60% | 122 | 40% |
| 3 comorbid conditions | 245 | 19.8% | 149 | 60.8% | 96 | 39.1% |
| 4 comorbid conditions | 113 | 9.1% | 61 | 53.9% | 52 | 46.1% |
| 5 or more comorbid conditions | 56 | 4.5% | 21 | 37.5% | 35 | 62.5% |
| Cases of in-hospital mortality | 315 | 25.5% | 196 | 62.2% | 119 | 37.7% |

into a single category, and the score was devised as 0 – no relevant comorbidities, 1 – single comorbidity, 2 – two comorbidities, 3 – three comorbidities, 4 – four or more relevant comorbid conditions (Table 2). To determine the relationship between the presence of comorbid conditions and age in our sample, we conducted Kendall's tau correlation – the result showed a strong positive relationship between the score and age, with $\tau b$ of 0.320 and associated p-value below 0.0001. [18]. From 305 patients with score of at least 3, 47.8% were cases of in-hospital mortality. The distribution of scores among different age groups is presented in Table 4.

**Table 2.** *Comparison between deceased and discharged patients.*

| Variable | N = 1237 | Discharged, 922 | | Deceased, 315 | | Associated p-values |
|---|---|---|---|---|---|---|
| Age, median, IQR | 65 | 62 | 18 | 73 | 15 | 0.000 |
| Age category, 16-55 y, % | 336 | 312 | 33.8% | 24 | 7.6% | |
| 56-65, % | 312 | 252 | 27.3% | 60 | 19% | |
| 66-73, % | 291 | 206 | 22.3% | 85 | 26.9% | |
| 74 or more years, % | 298 | 152 | 16.5% | 146 | 46.3% | |
| Gender, males | 746 | 550 | 59.7% | 196 | 62.2% | 0.421 |
| Gender, females | 491 | 372 | 40.4% | 119 | 37.8% | |
| Length of stay, days | | 12 | 5 | 4 | 8 | 0.000 |
| No comorbidities | 198 | 183 | 19,9% | 15 | 4.8% | 0.000 |
| Arterial hypertension | 776 | 540 | 58.6% | 236 | 74.9% | 0.000 |
| Diabetes mellitus | 338 | 215 | 23.3% | 123 | 39.1% | 0.000 |
| Malign diseases | 77 | 55 | 5.9 % | 22 | 6.9% | 0.083 |
| Chronic respiratory conditions | 156 | 107 | 11.6% | 49 | 15.6% | 0.068 |
| Chronic cardiological conditions | 293 | 168 | 18.2% | 125 | 39.7% | 0.000 |
| Hematological conditions | 74 | 37 | 4% | 37 | 11.8% | 0.000 |
| Chronic kidney injury | 114 | 56 | 6.1% | 58 | 18.4% | 0.000 |
| Neurological sequelae | 192 | 103 | 11.2% | 89 | 28.3% | 0.000 |
| Thyroid disease | 90 | 67 | 7.3% | 23 | 7.3% | 0.984 |
| Gastrointestinal conditions | 210 | 153 | 16.6% | 57 | 18.1% | 0.540 |
| Score 0 | 248 | 230 | 28.2% | 18 | 7.3% | 0.000 |
| Score 1 | 367 | 304 | 32.5% | 63 | 17.2% | |
| Score 2 | 317 | 233 | 25.3% | 88 | 27.8% | |
| Score 3 | 211 | 104 | 11.3% | 93 | 44.1% | |
| Score 4 | 94 | 41 | 2.1% | 53 | 56.4% | |

The last analysis using binomial logistic regression for predicting in-hospital mortality revealed that age and gender remained robustly associated with the outcome in all models. In the basic model (model 1, age quintile and gender, Table 3), being male was associated with a 1.33 times increase in odds for in-hospital mortality (when compared to female patients), while being 74 years or older was associated in 13 times higher odds for in-hospital mortality, when compared to patients that were in the age range of 16 to 55 years. Further, models adjusted for age and gender revealed highest OR for presence of chronic kidney disease, followed by hematological diagnoses. The diagnosis for arterial hypertension, malign diseases, chronic respiratory conditions did not attain classic statistical significancy (p-values < 0.05, CI not including 1). Although univariate analysis suggested association of arterial hypertension with the outcome, this association lost significance in the adjusted model. When using the sum score, the final model (Model 8, Table 3), showed that all categories of age, male gender and comorbid score were statistically significantly associated with the outcome. For instance, patients with 1 point have a 1.78 times increase for OR for in-hospital mortality when compared to those with 0 points; patients with 3 points have 5.4 times higher OR when compared to the reference group.

**Table 3.** *Results from the binomial logistical regression, models adjusted for age and gender.*

| Model | Predictors | B | s.e | Wald | p-val. | Exp(b) | 95%CI, LB | 95%CI, UB |
|---|---|---|---|---|---|---|---|---|
| 1 (Base) | 16-55 y (ref) | | | 133.040 | 0.000 | | | |
| | 56-65 | 1.140 | 0.256 | 19.783 | 0.000 | 3.126 | 1.892 | 5.165 |
| | 66-73 | 1.693 | 0.248 | 46.486 | 0.000 | 5.438 | 3.342 | 8.847 |
| | 74 or more years | 2.566 | 0.243 | 111.538 | 0.000 | 13.009 | 8.081 | 20.942 |
| | Gender, male | 0.291 | 0.145 | 4.028 | 0.045 | 1.338 | 1.007 | 1.779 |
| 2 | Arterial hypertension | 0.232 | 0.161 | 2.065 | 0.151 | 1.261 | 0.919 | 1.729 |
| 3 | Diabetes mellitus | 0.665 | 0.150 | 19.578 | 0.000 | 1.945 | 1.449 | 2.612 |
| 4 | Cardiological diagnoses | 0.679 | 0.154 | 19.534 | 0.000 | 1.972 | 1.459 | 2.665 |
| 5 | Hematological diagnoses | 1.170 | 0.265 | 19.510 | 0.000 | 3.221 | 1.917 | 5.411 |
| 6 | Chronic kidney disease | 1.215 | 0.218 | 31.203 | 0.000 | 3.371 | 2.201 | 5.164 |
| 7 | Neurological conditions | 0.856 | 0.175 | 23.877 | 0.000 | 2.353 | 1.669 | 3.316 |
| 8 | 16-55 (ref) | | | 81.293 | 0.000 | | | |
| | 56-65 | 0.780 | 0.266 | 8.612 | 0.003 | 2.182 | 1.296 | 3.674 |
| | 66-73 | 1.182 | 0.261 | 20.488 | 0.000 | 3.261 | 1.955 | 5.441 |
| | 74 years or more | 2.036 | 0.255 | 63.604 | 0.000 | 7.657 | 4.643 | 12.627 |
| | Gender, male | 0.365 | 0.151 | 5.845 | 0.016 | 1.441 | 1.072 | 1.937 |
| | 0 points (ref) | | | 67.66 | 0.000 | | | |
| | 1 point | .578 | 0.294 | 3.864 | 0.049 | 1.782 | 1.002 | 3.169 |
| | 2 points | 1.075 | 0.290 | 13.734 | 0.000 | 2.929 | 1.659 | 5.172 |
| | 3 points | 1.698 | 0.297 | 32.626 | 0.000 | 5.461 | 3.050 | 9.778 |
| | 4 points | 2.122 | 0.342 | 38.610 | 0.000 | 8.352 | 4.276 | 16.313 |

**Table 4.** *Distribution of scores by age group*

| Score | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 16-55 years | 143 | 113 | 54 | 21 | 5 |
| %* | 57.7% | 30.8% | 17.0% | 10.0% | 5.3% |
| 56-65 years | 57 | 103 | 78 | 59 | 15 |
| %* | 23.0% | 28.1% | 24.6% | 28.0% | 16.0% |
| 66-73 years | 33 | 67 | 101 | 56 | 34 |
| %* | 13.3% | 18.3% | 31.9% | 26.5% | 36.2% |
| 74 or more years | 15 | 84 | 84 | 75 | 40 |
| %* | 6.0% | 22.9% | 26.5% | 35.5% | 42.6% |

*From all patients with the same score

## DISCUSSION

The presented study is the first study from our country that reveals our experience with this novel condition. During the observation period of the study, there were 75,293 incident cases of SARS-CoV-2 infections and 2254 cases of SARS-CoV-2 associated cases of mortality at a national level, while our sample registered 13.97% of all cases of mortality during this period. The study population presented were patients with limited access to ICU during the peak of the pandemic; hence, unlike most of the studies that report on cohort of patients with access to invasive ventilation and other forms of ICU care, our sample is comparable to the reports by [19]–[21] in terms of care.

The use of EHRs in our case was performed without previous investigations on its validity, hence a pilot procedure was conducted. There (Supplement 2), the procedure showed an excellent level of agreement, with the lowest level of agreement being for chronic gastrointestinal conditions [22]. Additionally, all comorbid groups were sufficiently present in the sample, with the exception of the diagnosis of obesity (see paragraph below). From the whole sample, 189 patients without a single diagnosis were within the median age range of 53 (IQR – 21), while patients with any comorbidities were older, with a median age of 66 (IQR – 18). The findings for the prevalence of certain comorbidities were expected; arterial hypertension was the most prevalent in the sample, followed by diabetes mellitus. The raw sum score and the final score showed a positive relationship (Table 4) to age. The scores derived from the diagnoses showed expected association to in-hospital mortality (Table 2).

The results reaffirm the findings that age is a robust predictor of in-hospital mortality and worse outcomes in SARS-COV-2 [23], [24]. In our case, we defined the baseline age category as at-risk people between the ages 16 to 55 years old, while the other three groups showed an increasing OR for in-hospital mortality. Males had worse outcomes with COVID-19 disease, and this was replicated in our study. In the first model, being male was associated with a 38% increase in OR for the outcome, while in the final model (adjusted for age and score), this association rose to 44% increase in OR. A recent meta-analysis by Pijls et al. [24] reports that males have a higher relative risk for dying than females, by 50% (95%CI 1.18-1.91). The connection between the gender and these outcomes is topic of current studies, with several feasible explanations offered[25].

The presence of arterial hypertension was a cause for concern at the beginning of the pandemic [26], with problematic associations due to postulated endothelial effects [27] or due to the effects of some medications for arterial hypertension. Wide meta-analysis [4] points out that this association vanishes after the adjustment for the effects of age and gender, and some health authorities do not regard it as an independent risk factor for disease severity and worse outcomes [28]. The results from our study suggest that patients with arterial hypertension do not have a substantially higher risk for in-hospital mortality, when taking into regard gender and age. Contrasting with that, the presence of chronic cardiac conditions, such as heart failure, certain dysrhythmic conditions or conditions after invasive cardiac procedures are significant predictors, and this agrees with previous findings, such as [29], [30].

With diabetes mellitus, the national estimate points out that the prevalence of diagnosed patients is 5%, with an estimated diagnostic rate of 44.8% [31] on a national level. In our study, of all 1237 patients, 27.3% were already diagnosed with diabetes mellitus upon admission, while this figure was 39.1% for the deceased patients, representing a stark difference. The association proved robust after adjusting for the effects of gender and age, with an associated 1.94 times increase in odds ratio for hospital mortality. A recent meta-analysis revealed that patients with diabetes mellitus had a two-fold risk increase in mortality, as well an increased risk for contracting the disease and ICU admission [32].

The presence of chronic kidney disease was associated with the highest increase in the unadjusted and adjusted odds for mortality, when compared to other comorbidities. These associations were previously known and reported by different studies [33]. Regarding patients with chronic kidney injury, it has been previously reported that there is striking rise in hospital mortality in these patients during the first 6 months of the pandemic [34]. As such, both findings alert to the possibility that a special approach towards these patients is warranted and should provoke additional investigation into the possible pitfalls of epidemiological measures, diagnoses or care of these patients.

A diagnosis for respiratory conditions or active malignancy did not show any robust association in the baseline analyses and did not produce any statistically significant OR in the adjusted models. A systematic review of patients with COPD, but not asthma, are a special at-risk group [35], revealing a higher mortality risk since the start of the pandemic [36]. In observing the associated risks of malignancy, past and current diagnosis for malignancy was found to be related to worse outcomes [29], although there are studies that did not find an association for solid malignancies [37]. Therefore, the lack of such associations in our study might stem from our general approach (categorizing both patients with asthma/COPD in a single group, see details in Supplement 2). Additionally, the presence of hematological malignancy produced the second highest OR increase (see Table 3), although these patients were coded as having hematological diagnosis, but not malignancy (to avoid double coding).

The choice of the comorbidities reflected the knowledge on their impact on the clinical course of COVID-19 pneumonia and by taking diagnosis registration practices into regard. For instance, the variable on obesity (E66 by ICD-10) did not show any association to mortality and only 6.4% (79 patients) of the sample had that diagnosis. This is also discordant with the presence of diabetes mellitus, which was present in 27.3% of the sample. Additionally, the Public Health Institute issued that 19.6 % of the males and 17.2 % of the females fulfil BMI criteria for obesity at national level (available in Macedonian). The current EHRS does not capture data on weight or height, and it was not possible to validate this diagnosis. Similarly, a Brazilian study encountered a similar problem, where it was decided to omit this variable from further analysis [38]. The diagnosis for hypothyroidism and gastrointestinal conditions were used knowing that there were no known associations with COVID-19 at the time [39], and it used to check if data collection procedure was robust. As expected, results from the comparisons did not reveal any increased odds for in-hospital mortality in patients with hypothyroidism or gastrointestinal conditions.

The attempts to create a score as a sum of relevant comorbid conditions for the purpose of stratifying patients according to risk were with limited success. The observation that having at least three comorbid conditions used in the score prior the diagnosis is associated with a substantial risk for in-hospital mortality (above 50%), thereby suggesting that such an approach is feasible. The use of the score produced robust findings, when adjusted for the effects of age and gender, such as dose-response increment. Still, the predictive value reached its height at 76.2% overall correct classification, possibly due to the number of deceased patients that did not have any diagnosis. Improvement of this type of approach would be possible by using a more specific approach towards specific diagnostic groups, by using additional validation procedures, such as better diagnosis ascertainment (that could not have been met with this study) and by taking the intensity of the comorbidity and possibly its duration into consideration.

The main limitations of this study stem from the limited observation period, restricted to hospital stay, ignoring the intensity and duration of the diagnosis and the comorbid conditions, and idiosyncrasies related to the practice of recording diagnosis in the EHRs of the patients. Although the sample is representative on a national level, its generalizability could be limited by two factors, 1) availability of vaccinations and 2) emergence of new variants of the virus.

The practical findings of the study reveal multiple points for improvement of the national EHRS, as well as specifically pointing out the risks for in-hospital mortality according to age groups, gender, and the presence of certain comorbid conditions from a large unvaccinated sample. Patients with developed chronic kidney disease and hematological malignancy demand special attention in epidemiological approach and care, as these groups of patients showed the highest risk for in-hospital mortality in our study.

## CONCLUSION

The electronic records of the patients showed that the number of pre-existing diagnoses, male gender, and age as significant predictors for COVID-19 associated mortality. From all the available diagnoses, the diagnosis for chronic kidney failure showed strongest association with the outcome of interest, while the presence of arterial hypertension did not show any significant correlation.

## SUPPLEMENT 1

*Description of the background population and setting*

The presented study was conducted in PHI Clinical Centre Mother Theresa, with participation from 8 teaching hospitals (PHI UC for Pulmonology and Allergology, PHI Institute for Tuberculosis and respiratory conditions, PHI UC for Neurology, PHI UC for Dermatovenerology, PHI UC for Nephrology, PHI UC for Gastroenterohepatology, PHI UC for Otorhinolaryngology, PHI UC for Ophtalmology). The above-mentioned clinics were repurposed for care for patients with SARS-CoV-2 pneumonia during the second and third peak of the pandemic and started admitting patients on 06-11-2020. All hospital sites were supplied with system for central oxygen delivery with maximal flow rate of 16 l/min of O2 and portable oxygenators with maximal flow rate of 8 l/min of O2, without access to invasive ventilation OR extracorporeal membrane oxygenation (ECMO) therapy. Treatment was administered by specialist for internal medicine or respiratory pathology; all patients received at some point supplemental oxygen and course of corticosteroid therapy (methylprednisolone OR dexamethasone) and vast majority (above 90%) received course of antibiotic therapy and completed a course of anticoagulant therapy. Since most of the specific antiviral treatments were with sparse provisions at the height of the pandemic, only small portion of the patients received timed course of remdesivir, favipiravir, tocilizumab or convalescent plasma (below 5%). The hospital site did not have intensive-care unit and only one portion of the patients with severe disease were successfully transferred to facilities with ICU due to limited ICU bed capacities. Since March 2021, the hospital wards received equipment for non-invasive ventilatory support. The COVID-19 centers closed on 21.05.2021, with treated approximately 1700 patients with SARS-CoV-2 illness. Of note is however that this publication is part of broader study (that includes patients from the whole period) that investigates the patterns of mortality in hospital conditions and the associated laboratory antecedents that were collected as part of the care.

## SUPPLEMENT 2

*Selection of diagnoses for analysis from the national electronic health records system MojTermin*

The national electronic health records system MojTermin was commenced in 2012 [1]. Since then, every public healthcare provide uses this system to record patient data on visits, hospital stay, demographic details, allergic conditions and chronic comorbid conditions and drug prescriptions. Initial study reported that there were 790705 patients registered in the time interval from 01.01.2014 to 01.06.2014, covering almost 42% of the closest population estimate (national census data Sep-2021, approximately 1900000 residents) in timeframe of 5 months. One pitfall is that private healthcare providers are not obliged to enter data on patient interaction, which is mostly pronounced for surgical patients seeking care. Thus, this limitation precludes inclusion of such diagnostic categories for the objective of the study. Another pitfall is that although that the health system coverage is free, substantial part of the population is unemployed and more likely not to attend their providers for regular health check-ups, while the employed are obliged to undergo systematic health check up on interval from 1 to 3 years, depending on the category. In addition, most of the referrals in MojTermin are for specialists for internal medicine (and for chronic conditions, making it more suitable for these types of comorbidities. On the basis of previous reports, idiosyncrasies EHRS and expected prevalence of chronic comorbid conditions, it was decided that the following lists of diagnoses should be marked and retrieved from the EHR of the patients : arterial hypertension (defined as presence of diagnosis I-10 OR prescribed anti-hypertensives for longer than 6 months), diabetes mellitus (defined as presence of ICD-10 diagnosis E08-E13); active malignancy (defined as

ICD-10 codes C00-C96, excluding haematological conditions, marked in the last 5 years of diagnosis); obesity (defined as ICD-10 code E66) ; chronic respiratory conditions requiring therapy (defined as ICD-10 codes J40-J70, excluding upper respiratory conditions) ; chronic cardiac conditions requiring therapy or past cardiac interventions(defined as ICD-10 codes I05-I09, I20-I25, I30-I50, Z95) ; chronic haematological conditions requiring therapy (ICD-10 codes D55-D60, including haematological malignancies under C81-C96 and ill-defined and unspecified malignancies under C76-C80); chronic kidney disease requiring therapy or follow-up (ICD-10 codes N17-N19) ; chronic neurological sequelae or neurodegenerative disorders (defined as ICD-10 codes I65-I69, G20, G30-G32, G70-G73, G80-G83) ; thyroid disease requiring therapy (defined as ICD-10 codes E00-E06 and issued prescription of levothyroxine OR propylthiouracil) ; chronic gastrointestinal and hepatic condition requiring therapy (defined as ICD-10 codes K50-K52, K70-K77). Cases of specific neoplasm diagnoses of the respiratory, gastrointestinal, and nervous systems were counted as malignancies and not as chronic respiratory OR gastrointestinal OR neurological conditions, to avoid double counting. Cases were there was specific neoplasm of these organic systems and additional diagnosis from the same category, for instance malign neoplasm of the brain and hemiplegia, were counted as both active malignancy and presence of chronic neurological condition. Pilot study with a random sample of 44 cases and two independent raters blinded to outcome was conducted in March 2021, with results presented in the main text. For the main data collection procedure, seven physicians were instructed with the diagnosis definitions and did the collection process. Data on demographics, hospital stay, and outcomes were collected separately from data on comorbidities.

Data on comorbidities was drawn in pilot sample for 44 patients by two independent raters before commencing of the full data collection procedure. No disagreements were found for the following diagnostic groups: obesity, chronic respiratory conditions, active malignancies, chronic hematological conditions and malignancies, chronic kidney injury and presence of thyroid diseases and therefore, kappa was not estimated. For the diagnosis of arterial hypertension, there were two cases of disagreement (kappa 0,908 with 95%CI of 0,78 to 1); one case of disagreement for diabetes mellitus (kappa 0,944 with 95%CI of 0,84 to 1) ; one case of disagreement for chronic cardiac conditions (kappa 0,927 with 95% CI from 0,78 to 1); one case of disagreement for chronic neurological sequelae or chronic neurological conditions (kappa 0,927 with 95%CI from 0,78 to 1) and two cases of disagreement for chronic gastrointestinal conditions (kappa 0,861 with 95% CI from 0,68 to 1).

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**Резиме**

## КОМОРБИДНИ СОСТОЈБИ ВО КОХОРТА НА ПАЦИЕНТИ ЛЕКУВАНИ ЗА САРС-КОВ-2 И НИВНАТА ПОВРЗАНОСТ СО БОЛНИЧКИОТ МОРТАЛИТЕТ ВО РАНАТА ФАЗА НА ПАНДЕМИЈАТА

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**Вовед**: Претходните студии покажаа дека возраста и коморбидниот профил на пациентите се поврзуваат со полоши исходи кај пациенти што се лекуваат за болест асоцирана со КОВИД-19. Целта на студијата е да утврди кои хронични заболувања се асоцирани со болничкиот морталитет во оваа група пациенти.

**Материјали и методи**: Се работи за студија на пресек на пациенти што имале потреба од болничко лекување поради состојба стекната од SARS-CoV-2. Студијата вклучува кохорта на пациенти лекувани од 6.11.2020 г. до 15.3.2021 г. За утврдување на коморбидниот профил беа прегледани електронските регистри на пациентите.

**Резултати**: Беа разгледани истории од 1468 пациенти, од кои 1237 ги исполнуваа критериумите за случај. Медијаната возраст на примерокот беше 65 години. Болничкиот морталитет изнесуваше 25,5 %, додека медијаната на престој изнесуваше 11 дена. Од целиот примерок, 16 % од пациентите немаа податок за каква било дијагноза во својот електронски картон, додека најчесто сретнувана дијагноза беше артерискaта хипертензија (62,7 %), по што следува дијабетес мелитус (27,3 %). Возраста, машкиот пол и бројот на дијагнози покажаа значително повисоки OR (3,37) за болнички морталитет. Присуството на хронична бубрежна болест покажа најсилно поврзување со болничкиот морталитет во овој примерок.

**Клучни зборови**: сарс-ков-2, пандемија, хронични заболувања, коморбидитети, болнички морталитет