Mortality of hospitalized patients with COVID-19: Effects of treatment options (vitamin D, anticoagulation, isoprinosine, ivermectin) assessed by propensity score matching, retrospective analysis

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Introduction. SARS-CoV-2 respiratory infection is associated with significant morbidity and mortality, especially in hospitalized high-risk patients. We aimed to evaluate the effects of treatment options (vitamin D, anticoagulation, isoprinosine, ivermectin) on hospital mortality in non-vaccinated patients during the 2021 spring wave in the Czech Republic.

Methods. Initially, 991 patients hospitalized in the period January 1, 2021, to March 31, 2021, with PCR-confirmed SARS-CoV-2 acute respiratory infection in two university and five rural hospitals were included in the study. After exclusion of patients with an unknown outcome, a total of 790 patients entered the final analysis. The effects of different treatments were assessed in this cohort by means of propensity score matching.

Results. Of the 790 patients, 282 patients died in the hospital; 37.7% were male and 33.3% were female. Age, sex, state of the disease, pneumonia, therapy, and several comorbidities were matched to simulate a case-control study. For anticoagulation treatment, 233 cases (full-dose) vs. 233 controls (prophylactic dose) were matched. The difference in mortality was significant in 16 of the 50 runs. For the treatment with isoprinosine, ivermectin, and vitamin D, none of the 50 runs led to a significant difference in hospital mortality.

Conclusion. Prophylactic-dose anticoagulation treatment in our study was found to be beneficial in comparison with the full dose. Supplementation with vitamin D did not show any meaningful benefit in terms of lowering the hospital mortality. Neither ivermectin nor, isoprinosine was found to significantly decrease hospital mortality.

Key words: SARS-CoV-2, COVID-19, vitamin D3, ivermectin, Isoprinosine, mortality, anticoagulation, propensity score matching

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INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has had a devastating impact worldwide, both in terms of patient mortality and economic losses. By the end of 2022, almost 700 million people were infected and 6.7 million died of COVID-19 or its complications[1]. Infection fatality rate was age dependent[2-5]. Accumulation of risk factors such as hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, and chronic kidney disease (CKD) lead to an increased risk of adverse outcomes of COVID-19 (ref.[6]). The presence of at least 2 risk factors was associated with increased mortality, irrespective of age and sex[7]. In a systematic review, patients suffering from CKD had the highest risk of mortality from COVID-19, followed by patients suffering from diabetes, hypertension, and cardiovascular diseases. Interestingly, current smoking posed an increased risk of disease severity but not higher mortality risk in itself[8].

The disease severity was also influenced by the individual immune response. Cardiovascular and other comorbidities may modify the immune response and thus aggravate the disease course and outcome[9]. Decreased

innate immune reactivity may result in higher viral load and, paradoxically, overreaction of the adaptive immune response. Adaptive immunity overreaction presented itself with proinflammatory cytokine spillover and increased D-dimer levels[10,11]. Immune overreaction and the "cytokine storm" were the targets of the host-directed treatment of COVID-19 (ref.[11]). It was shown that plasma vitamin D (cholecalciferol) levels were decreased in hospitalized patients with COVID-19 (ref.[12]). However, a recent systematic review of 27 trials demonstrated that vitamin D deficiency was not associated with a higher chance of SARS-CoV-2 infection, but severe cases of COVID-19 presented with vitamin D deficiency, compared with mild cases[13]. Moreover, vitamin D deficiency increased hospitalization and mortality rates in COVID-19 patients[13]. Besides vitamin D, there were several other treatment options such as ivermectin and isoprinosine, which may both have influenced the outcome. Isoprinosine was studied both in influenza-like viral respiratory infection and in COVID-19 patients, with the latter showing an earlier clinical response[14,15].

Summarizing the evidence, COVID-19 infection promotes a prothrombotic state and increases the risk for thromboembolic events[6,11]. In hospitalized patients with COVID-19, pulmonary embolism (19%) and venous thromboembolism (25%) was also the most frequent car-

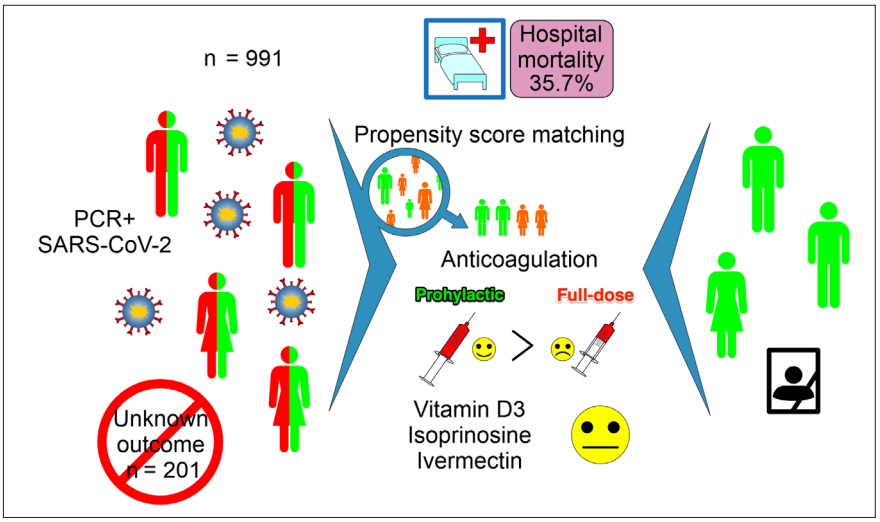

Fig. 1. Graphical abstract.

Table 1. Baseline characteristics of the study population.

	Total population n=991	Male n=549 (55.4%)	Female n=442 (44.6%)	*P*
Age (years)	69 ± 13.3	68±13.2	71.2 ± 13.3	0.001
Body weight (kg)	84.3 ± 27.2	90 ± 24.3	78 ± 29.6	0.039
Body height (cm)	166.7 ± 25.4	172.7 ± 23.3	158.7 ± 25.9	0.4
Body mass index (kg/m^2)	28.8 ± 9.5	28.3 ± 8.3	29.3 ± 10.9	0.001
Coronary artery disease	27.4	29.5	24.9	0.115
Atrial fibrillation	18.2	16.6	20.1	0.159
Hyperlipoproteinemia	40.1	39.7	40.5	0.845
Unilateral pneumonia	10.5	10	11.1	0.06
Bilateral pneumonia	75.9	78	73.3	0.172
Hypertension	72.1	70.7	74	0.255
Cancer	11.5	12.6	10.2	0.271
Diabetes mellitus	36.1	36.1	36.2	1
Previous stroke/TIA	10.9	12	9.5	0.22
COPD	20.9	19.1	23.1	0.136
CKD	15.5	16.6	14.3	0.333
Mechanical ventilation	18.5	21.9	14.3	0.001
HFNC	17.9	19.9	15.4	0.001
Oxygen therapy	47.6	32	48	0.656
Anticoagulation	94.6	93.6	95.7	0.162
Antibiotics	88.2	90	86	0.09
Corticosteroids	76.5	79.1	73.3	0.035
Lymphopenia	67	68.9	64.7	0.114

Table 2. Comorbidities of the selected cohort of 790 patients with respect to outcome.

	Present in deceased (n)	Present in deceased (fraction)	Present in recovered (n)	Present in recovered (fraction)	*P*
Total	282	1.00	508	1.00	
Lymphopenia	228	0.81	311	0.61	<0.001
Hypertension	220	0.78	338	0.67	<0.001
Dyslipidemia	126	0.45	184	0.36	0.020
Ischaemic heart disease	109	0.39	102	0.20	<0.001
Previous stroke	45	0.16	36	0.07	<0.001
Chronic pulmonary obstructive disease	73	0.26	87	0.17	0.003
Chronic kidney disease	67	0.24	55	0.11	<0.001
Diabetes mellitus	131	0.46	151	0.30	<0.001
Atrial fibrillation	79	0.28	69	0.14	<0.001
Current cancer	38	0.13	52	0.10	0.170

diovascular complication compared to heart failure (2%) or myocardial infarction (4%) (ref.[8]). It is thus crucial to what extent hospitalized COVID-19 patients should be anticoagulated.

Therefore, in this retrospective study, we analyzed whether anticoagulation treatment and/or vitamin D supplementation was effective in decreasing hospital mortality and we used propensity score matching. We similarly analyzed other treatments, including ivermectin and isoprinosine.

METHODS

Patients

The dataset covers 991 patients (see Table 1) hospitalized in the period January 1, 2021, to March 31, 2021, with COVID-19 in the following Czech hospitals: University Hospital Ostrava (Dept. of Internal Medicine and Cardiology, Dept. of Pulmonary Disease and Tuberculosis, and Clinic for Infectious Diseases), General University Hospital Prague, Ostrava City Hospital Fifejdy, Krnov Associated Medical Facilities, and the Havířov, Bílovec, and Třinec regional hospitals. COVID-19 infection was confirmed by the polymerase chain reaction test from the nose swab detecting SARS-CoV-2 ribonucleic acid. In the pandemic after confirmation of SARS-CoV-2 positivity in the presence of clinical respiratory infection, the patient was isolated and treated as a COVID-19 positive patient. Other diagnostic and treatment modalities were utilized solely based on the development of other symptoms. The standard of care was only oxygenation support; the level (i.e., HFNC, mechanical ventilation) was based on patient symptoms. Antibiotics were administered in case of CRP or procalcitonin elevation; no antivirotics, antibiotics, nor glucocorticoids were standard of care; if administered, the decision was at the discretion of the treating physician.

The data from all patients were collected between November 2021 to May 2022. The authors have access to the information that could identify individual participants, but only from their home institutions. Participants from other institutions added to the final dataset were anonymized.

There were three possible outcomes of hospitalization: death, discharge for recovery, and transfer to another facility. Patients may have been transferred to long-term care facilities or to less-intensive care units. Since we do not have data on the outcomes of the transferred patients, these were excluded from further analysis, leaving 790 patients. Patient characteristics are summarized in Tables 1 and 2. In addition to the data in Table 1, records on comorbidities and treatment strategies were also known. Comorbidities are summarized in Table 2. The treatment strategies differed across the five hospital centers. Treatment decision including all the treatment options were made at the discretion of the treating physician.

The study was approved by the Institutional Review Board of the University Hospital Ostrava (Nr. 967/2021), which also covered the rural hospitals and the General University Hospital in Prague. The study was conducted in accordance with the more recent Helsinki Declaration. All procedures were performed in accordance with the relevant guidelines. The need for informed consent was waived for the study by the Institutional review board of the University Hospital Ostrava.

Statistical Analysis

Continuous variables are expressed as means ± standard deviation and compared using the *t*-test or Mann-Whitney U test, as appropriate. Categorical variables are expressed as percentages and compared by the chi-square test or Fisher's exact test, as appropriate. Due to very significant association between the overall state of the patient and the treatment options, we used propensity score matching (PSM). To untangle the effect of a particular treatment option, we decided to simulate a case-control study on these retrospective data by means of propensity score matching. Thus, we chose a particular treatment – supplementation with vitamin D, see below – and matched each case (a patient who received it) to a unique control (a patient who did not receive it). The list of parameters that were matched exactly was different for each treatment option (details below). Age was matched

within 5 years; the remaining parameters are categorical and were matched exactly. If no match was found for a particular case, the case was excluded from the analysis. If more matches were found for a single case, a single match was selected randomly. The matching process was repeated 50 times for each treatment option to understand the underlying variability of the matched cohort. The difference in hospital mortality between the cases and controls was assessed by means of a chi-square test in a 2 × 2 contingency table. The 50 repetitions are naturally not independent, because most of the cases had a unique control. We evaluated the effect of the treatment modality by inspecting the consensus of the 50 repetitions.

The variables for matching were selected based on univariate significance in predicting hospital mortality and clinical relevance as a classical cardiovascular and morbidity/mortality risk factor. The matching variables were selected from the following list:

- Age (matched within 5 years; that is, the controls were selected so that the difference in age between a case and control did not exceed 5 years)
- State of the disease at hospital admission was based on general status, but mainly on the need for oxygen therapy, following three categories that were matched exactly: mild, moderate, and severe.
- Sex
- Pneumonia: unilateral, bilateral, or without pneumonia
- Therapy: The mode of oxygen therapy had the following four categories that were matched exactly: no need for oxygen therapy, oxygen mask, high-flow nasal cannula, mechanical ventilation
- Hypertension (HT)
- Ischemic heart disease (IHD)
- Diabetes mellitus (DM)

To check the reported in-house method of matching for the most important covariates, we also performed full standard propensity score matching. For each treatment modality, we build a logistic regression model that uses all 19 available predictors (age, gender, BMI, state of the disease, pneumonia, the mode of oxygen therapy, peak CRP, procalcitonin level, leucocyte count, and all the possible comorbidities listed in Table 2) to predict the probability of being in the treatment group. For each patient in the treatment group, we select a control with the closest propensity score. By means of a chi-squared test, we compared the proportions of the deceased in both the groups.

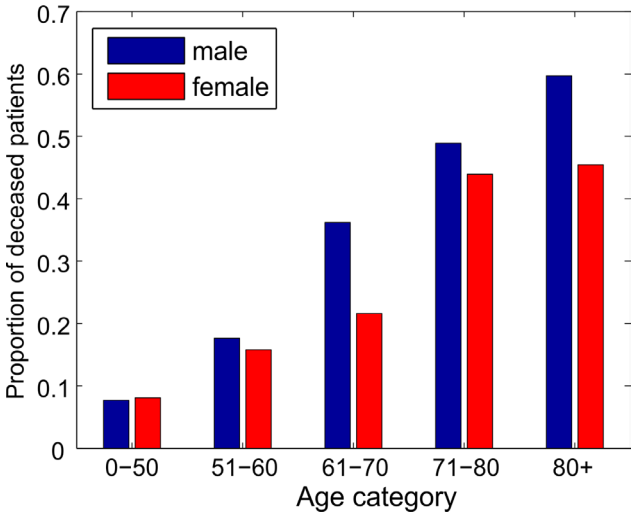

Fig. 2. Patient outcome in absolute numbers dismissed vs. deceased sorted by age groups for both males and females.

All the calculations were performed in IBM SPSS version 22 for MAC (IBM corp., Armonk, NY, US) or MATLAB version R2022b (MathWorks Inc., US).

RESULTS

Out of 790 patients included in the analysis, 282 (35.7%) patients died in the hospital; 162/430 (37.7%) were male and 120/360 (33.3%) were female (see Fig. 1). The mortality of men and women was not significantly different (P=0.20) in general. When broken down by age groups (Fig. 2), the most profound difference (36.2% of males vs. 21.6% of females deceased) was found in the age group 61–70 years. The difference is significant (P=0.05). Age and gender distribution of the cohort is depicted in Fig. 3. Men and women differed significantly in anthropometric parameters, age, and ventilation modalities used (Table 1).

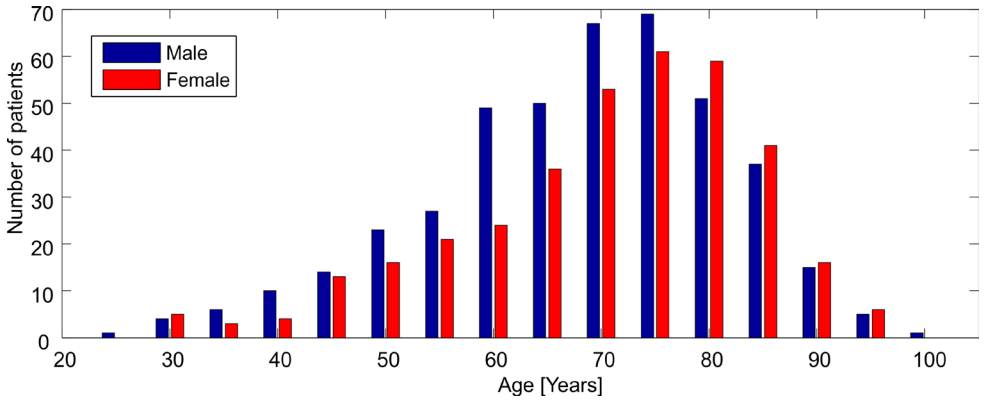

Fig. 3. Distribution of age and gender in the cohort with bin size = 5 years.

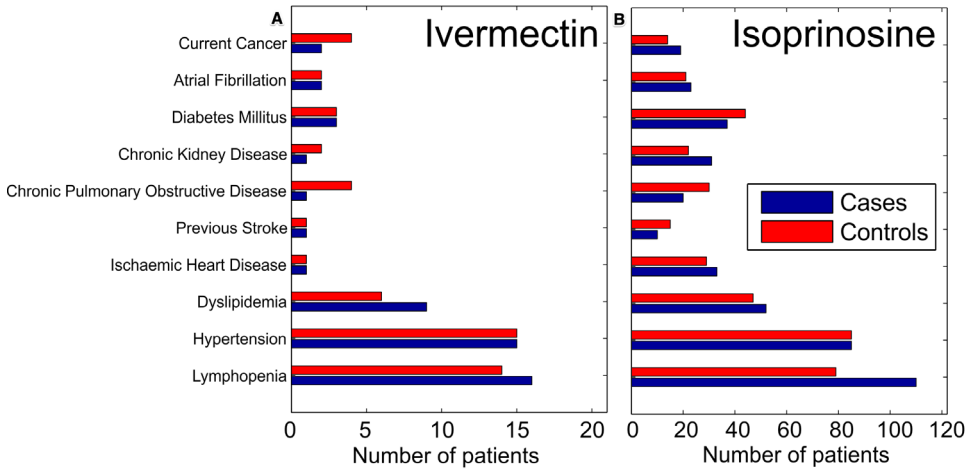

Fig. 4A. Twenty-one cases (treated with ivermectin) were balanced for the most important clinical parameters (y-axis) with 21 controls (not treated with ivermectin) constituting the propensity score matching cohort for ivermectin.
Fig. 4B. One hundred thirty-seven cases (treated with isoprinosine) were balanced for most important clinical parameters (y-axis) with 127 controls (not treated with isoprinosine) constituting the propensity score matching cohort for isoprinosine.

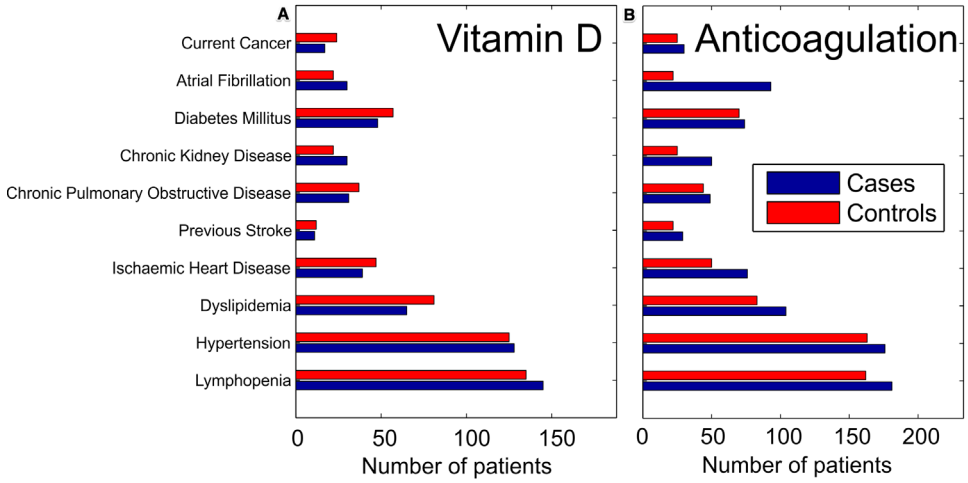

Fig. 5A. One hundred ninety-eight cases (treated with vitamin D) were balanced for the most important clinical parameters (y-axis) with 171 controls (not treated with vitamin D) constituting the propensity score matching cohort for vitamin D.
Fig. 5B. Two hundred thirty-three cases (full-dose anticoagulation) were balanced for the most important clinical parameters (y-axis) with 233 controls (prophylactic dose) constituting the propensity score matching cohort for anticoagulation.

The average dose of vitamin D in our study was 4650 ± 770 ICU/day, median 3000 ICU/day, and a total of 198 patients were treated with vitamin D.

Predictors of hospital mortality

In a univariate analysis, almost all predictors were significantly associated with death from COVID-19. It is more interesting to notice the predictors that did not show a significant association: BMI and sex showed no effect. Among the comorbidities, only the presence of cancer did not seem to be associated with death from COVID-19. Among the treatment modalities, ivermectin, isoprinosine, and vitamin D were not associated with in-hospital COVID-19 mortality. However, the univariate analysis did not provide much insight because the treatment modalities are naturally very dependent on the states of the patients and their comorbidities.

Propensity score matching

Ivermectin treatment

First, we concentrated on ivermectin treatment in the standard dosing of 0.2 mg/kg or, in obese patients, 0.3–0.4 mg/kg, administered for a minimum of 2 days. There were 28 cases treated with ivermectin. For these, we

decided to match the following characteristics exactly: age (within 5 years), sex, state, pneumonia therapy, HT, IHD, and DM (see Fig. 4A). With the above matching criteria, 21 cases could be matched to controls, and in some cases several controls were possible. Among the 21 matched cases, 5 patients (24%) died, and among the controls, a median (across the 50 repetitions) of 6 patients died. The difference was not significant in any of the 50 runs. Thus, treating patients with ivermectin does not seem to affect their hospital mortality significantly. The full standard logistic regression-based propensity score matching (FSLR-PSM) confirmed the lack of effect (P=0.17).

Isoprinosine treatment

The same methodology was then applied to treatment with isoprinosine. Isoprinosine was administered orally, 1 g every 6 hours per day. There were 137 cases in the dataset. We matched for age (within 5 years), sex, state, pneumonia therapy, and HT (see Fig. 4B). A total of 122 controls were found in each of the 50 runs. Among the 122 matched cases, 50 patients (41%) died, and among the controls, a median (across the 50 repetitions) of 50 patients died (41%). The difference was not significant in any of the 50 runs. Double checking with the FSLR-PSM confirmed the lack of any effect (P=0.46). Thus, treating patients with isoprinosine did not affect hospital mortality significantly.

Supplementation with vitamin D

There were 198 cases in the dataset. We matched for age (within 5 years), sex, state, pneumonia, and therapy (see Fig. 5A). There were a total of 188 controls in each of the 50 runs. Of the 188 matched cases, 75 patients (40%) died, and of the controls, a median (across the 50 repetitions) of 75 patients died (40%). The difference was not significant in any of the 50 runs. With FSLR-PSM there was no difference with respect to vitamin D treatment (P=0.36). Thus, treating patients with vitamin D did not appear to reduce their hospital mortality significantly.

Anticoagulation

We matched for age (within 5 years), sex, state, pneumonia, and therapy (see Fig. 5B). Forty patients completely without anticoagulation therapy were excluded from this analysis. We thus compared only patients with full anticoagulation therapy (cases) to patients with prophylactic anticoagulation treatment (controls). A total of 233 controls were found in each of the 50 runs. Among the 233 matched cases, 118 patients (51%) died, and among the controls, a median (across the 50 repetitions) of 100 patients died (43%). The difference was significant in 16 of the 50 runs. Thus, there is some evidence, albeit weak, that prophylactic anticoagulation treatment might have been a better option than full-dose anticoagulation in the hospitalized patients with COVID-19. The proportion of deceased among those on complete anticoagulation therapy with the FSLR-PSM was 51% while the proportion of deceased among controls (on prophylactic therapy) was only 33%. This difference is highly significant (P<0.001). This confirms the results of the direct matching strategy.

DISCUSSION

The main findings of our retrospective analysis may be summarized as follows:

1) Vitamin D supplementation did not have any meaningful effect on in-hospital mortality.
2) Neither isoprinosine nor ivermectin had any effect on in-hospital mortality.
3) Prophylactic anticoagulation treatment was to some degree beneficial compared with the full dose anticoagulation.
4) Overall, 35.7% of patients died in the hospital: 37.7% males and 33.3% females, and the difference between sexes was not significant (except for the age group of 61–70 years.).

Vitamin D supplementation

There are other explanations for vitamin D supplementation not showing any meaningful effect on the mortality rate in patients with COVID 19. First, the doses were considerably lower than the recommended doses of at least 3335 to 5336 IU of vitamin D per day in adults with vitamin D3 malabsorption from different causes[16]. Second, if a patient died very early after admission, no meaningful effect could have been observed, because it takes time for this treatment to have effect.

In the COVIT-TRIAL, 254 patients were randomized to either a "standard dose" of vitamin D (50,000 IU) administered over 72 hours, or high-dose (400,000 IU) as a single oral dose. The early administration of high-dose vitamin D in older patients with at least one of the known risk factors (age ≥75 years, SpO_2≤94%, PaO_2/FiO_2≤300 mmHg) reduced overall mortality at day 14. The effect was no longer observed after 28 days[17]. In a sample of US veterans, vitamin D2 and D3 fills were associated with reductions in SARS-CoV-2 infection of 28% and 20%, respectively[18]. Mortality due to COVID-19 within 30 days was similarly 33% lower with vitamin D3 and 25% lower with vitamin D2 treatment[18]. Interestingly, black veterans benefited more from vitamin D supplementation in general than did their white colleagues[18]. However, except for these two trials, there is variable evidence of a positive association between vitamin D and COVID-19 outcomes[19]. From the meta-analysis and trial sequential analysis, vitamin D administration results in reduced risk of death and ICU admission[20]. All evidence suggests that vitamin D supplementation poses no harm in COVID-19 infection and may reduce the risk of mortality in older patients and black patients and that the effect is dependent on the dose.

Isoprinosine and ivermectin treatment

Isoprinosine (inosine pranobex, IP) is a synthetic compound with an immunomodulatory effect in the early phase of viral infection[21]. Previously, it was studied in the setting of acute viral infection of multiple etiology and was proven to be effective in a randomized placebo-controlled trial (RCT) in 50-year-old non-obese patients diagnosed with influenza-like illnesses[14]. In the COVID-19 population, IP showed significantly earlier clinical response

compared with placebo[15]. In our study, IP had no meaningful effect on mortality in hospitalized patients. However, there were significant differences between the RCT cohort and our cohort. First, our patients were much older, with significant cardiovascular and other comorbidities. Second, the treatment was started later than it was in the RCT setting, and we studied only the hard end point of overall mortality. We believe IP might be beneficial in younger patients and when administered early in the course of the SARS-CoV-2 respiratory infection. It is probably not helpful in elderly patients when their condition necessitates hospital admission.

In a meta-analysis of 95 studies, ivermectin showed reduced ICU admissions, lower hospitalization length, and better recovery and viral clearance, and most importantly it lowered mortality – these results, however, are neither peer reviewed nor published[22].

In contrast, in the RCT setting, treatment with ivermectin 0.4 mg/kg in the early phase of SARS-CoV-2 infection did not result in a lower incidence of hospital admissions or other beneficial effects[23]. Also, in our propensity matching analysis, ivermectin did not show any effect on hospital mortality as compared with that of paired controls.

Anticoagulation treatment

Among patients with COVID-19, the most common finding is elevated D-dimer, and this has been shown in many trials and from the very beginning of the COVID-19 outbreak[11]. Even though D-dimer is elevated in the absence of severe clinical symptoms, it is a marker of a prothrombotic state sensitive, but not specific for COVID-19 (ref.[24]). It is now well documented that COVID-19 poses an increased risk of thromboembolism (TE): in a meta-analysis the mortality was 23% in the TE+ group and 13% in the TE – group of COVID-19 patients[25]. According to the International Society for Thrombosis and Hemostasis guidelines, prophylactic doses of low-molecular-weight heparin are recommended for all patients requiring hospital admission due to SARS-CoV-2 infection, irrespective of disease severity[24]. Interestingly, chronic therapeutic anticoagulation treatment at the time of infection was protective in terms of thrombotic complications and reduced disease severity[26]. More importantly, however, full-dose anticoagulation reduced the need for vital organ support and also reduced mortality in moderately ill patients in the multiplatform randomized trials (ATTAC, ACTIVE-4a, REMAP-CAP) (ref.[27]). The same multiplatform randomized trials showed no benefit in critically ill patients in terms of longer survival or organ support–free days[28]. COVID-PACT RCT confirmed the need for full-dose anticoagulation, but not clopidogrel, in critically ill patients with COVID-19 (ref.[29]). This resulted in the reduction of thrombotic complications at the expense of bleeding with no apparent excess mortality[29]. In our propensity-matched analysis, prophylactic anticoagulation was associated with a marginally lower hospitalization mortality compared to the full-dose anticoagulation. Most of our patients reflected the non-critically ill patient group from the multiplatform trial but we also had critically ill patients[27]. This may probably explain the disparity of the outcome of lower mortality in the prophylactic-dose anticoagulation arm. We may also speculate, that the full dose anticoagulation was assigned to the more severely ill patient population and/or increased the risk of bleeding.

Limitations

This is a non-randomized, though propensity-matched, retrospective analysis limiting its results to nonrandom allocation to specific treatment. A low dose of vitamin D was used, in general. There was low utilization of isoprinosine and ivermectin. The treatment decision was at the discretion of the treating physician.

CONCLUSION

Supplementation with vitamin D did not show any meaningful benefit in terms of lowering the death rate among hospitalized nonvaccinated patients with COVID-19. However, this is far from being a proof of missing effect, since the doses used in our centers were low. Prophylactic anticoagulation treatment, in comparison with the full-dose dose, was associated with a slightly lower mortality.

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Conflicts of Interest Statement: The authors declare no conflict of interest.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request and in compliance with the General Data Protection Regulation. There are ethical restrictions on sharing data publicly, as our data sets contain potentially sensitive health care-related information. Due to the amount of data on each patient only pseudo-anonymization would be possible. Data requests can be sent to the local institutional review board (e-mail: eticka.komise@fno.cz)

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