Comparison of the Mortality of Non-COVID Hospitalized Patients during the COVID Pandemic: A Retrospective Cohort Study in a Tertiary Medical Center in Israel

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ABSTRACT **Background:** At the beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic presented a new burden on healthcare systems.

Objectives: To evaluate the impact of the COVID-19 pandemic on the outcome of non-COVID patients in Israel.

Methods: We conducted a retrospective observational cohort study at a tertiary medical center in Israel. From December 2018 until June 2022, 6796 patients were hospitalized in the internal medicine wards. Patients were grouped based on their admission date: admitted during COVID waves (waves group), admitted between waves (interim group), and admitted during the same months in the previous year (former-year group).

Results: Mortality during hospitalization and 30-day mortality were higher in the waves group compared to the interim and former-year groups (41.4% vs. 30.5% and 24%, 19.4% vs. 17.9% and 12.9%, $P < 0.001$). In addition, 1-year mortality was higher in the interim group than in the waves and former-year group (39.1 % vs. 32.5% and 33.4%, $P = 0.002$). There were significant differences in the readmissions, both at 1 year and total number. The waves group had higher rates of mechanical ventilation and noradrenaline administration during hospitalization. Moreover, the waves group exhibited higher troponin levels, lower hemoglobin levels, and more abnormalities in liver and kidney function.

Conclusions: Hospitalized non-COVID patients experienced worse outcomes during the peaks of the pandemic compared to the nadirs and the preceding year, perhaps due to the limited availability of resources. These results underscore the importance of preparing for large-scale threats and implementing effective resource allocation policies.

IMAJ 2023; 25: 655–661

KEY WORDS: coronavirus disease 2019 (COVID-19), epidemiology, health policy, hospitalization, internal medicine

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At the beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic presented a new burden on healthcare systems worldwide, including in Israel [1]. The first case of COVID infection was confirmed at our tertiary center in February 2020 [1]. One month later, the government began enforcing a social distancing policy, and shortly thereafter a national state of emergency was declared [2]. The Israeli healthcare system dealt with five epidemic waves from January 2020 until April 2022 [3]. During each wave, hospitals maintained designated COVID departments and/or intensive care units, which were mostly operated by teams from the internal medicine wards and intensive care units. Israel established a national database to share information on vaccines, COVID morbidity, and mortality [4,5]. Two years later, most of the restrictions related to the COVID pandemic were lifted or reduced [6,7].

THE IMPACT OF COVID ON PUBLIC HEALTH

Numerous studies have investigated the direct consequences of the COVID-19 pandemic on global morbidity rates [8-10]. However, less attention has been given to the indirect impact of a concurrent pandemic and its influence on other medical situations. Notably, a study conducted in Israel revealed a decline in surgical admissions, an elevated hospitalization rate, and increased morbidity and emergency procedures in acute care surgery units during the pandemic [11]. Similarly, a study conducted in the intensive cardiac care unit demonstrated a rebound effect in acute myocardial infarction, characterized by reduced daily admission rates during the early phase of the COVID-19 outbreak, followed by a subsequent increase in hospitalizations during the later phase. Specifically, the reduction primarily involved non-ST elevation myocardial infarctions, whereas the rebound increase was predominantly observed in cases of ST-elevation myocardial infarctions [12]. A study conducted in France reported a decrease in stroke alerts during the pandemic compared to the corresponding period the previous year. Despite the absence of a decline in stroke incidence, there was a notable decrease in patients presenting within the therapeutic time window [13].

The primary objective of our study was to assess the impact of the COVID-19 pandemic on non-COVID patients admitted to the internal medicine division of a tertiary center in Israel. To mitigate potential confounding factors related to season-

al admission fluctuations, we specifically examined mortality and morbidity among patients admitted during pandemic waves compared to those admitted between waves and during the corresponding months in the pre-pandemic years. We hypothesized that patients admitted during the waves would experience worsened clinical outcomes.

PATIENTS AND METHODS

In this retrospective study, we investigated a cohort of 6796 patients who were admitted to the internal medicine wards of a tertiary medical center between December 2018 and June 2022. The construction of the cohort was facilitated by employing the MDClone© data synthesis platform. Our study focused on patients aged 18 years and older who were admitted to eight internal medicine departments and two geriatric departments within the medical center. The primary objective of this study was to characterize the impact of the COVID-19 pandemic on overall mortality, with particular attention to the mortality rates of non-COVID patients during the pandemic period. The exclusion criterion was patients who had received a COVID-19 diagnosis at the time of admission, as determined by either a polymerase chain reaction test or an antigen test conducted on admission. Data utilized in our analysis were extracted directly from the electronic medical records of the patients. The institutional review board of Sheba Medical Center approved the study, ensuring the strict maintenance of participant anonymity during database analyses. This study was approved by the Sheba Medical Center Helsinki Committee, 8884-21-SMC.

STUDY DESIGN AND DATA COLLECTION

The cohort of patients in this study was stratified into three groups based on their admission date. The *waves* group comprised patients admitted during the specific COVID waves, which was defined by start and end dates obtained from the WHO database [3]. Two reference groups were established to provide comparative contexts: the *interim* group encompassed patients admitted between the waves, and the *former-year* group consisted of patients admitted in the same calendar months in the preceding year (2018). The detailed timeline and group divisions can be found in Supplemental Table A (available in the online version only). We identified and excluded 742 patients who were admitted on ambiguous dates that did not align with any specific wave or interim period (e.g., November 2021). Those 742 cases were annotated as missing and were not included in subsequent analyses. To account for co-morbidities and to assess patients' overall health status, we collected all necessary data to calculate the Charlson Comorbidity Index [14]. The index is a validated tool used to predict the expected 10-year survival and serves as an indicator of the co-morbidity burden of all included patients.

STATISTICAL ANALYSIS

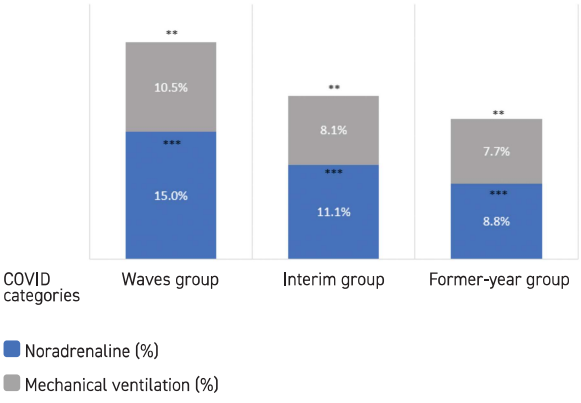
Comprehensive data regarding demographic characteristics, clinical parameters, and treatment variables were meticulously defined and collected for all enrolled patients. The primary outcomes under investigation included mortality during hospitalization, 30-day mortality, and 1-year mortality. In addition, readmissions within 30 days and 1 year as well as the cumulative total number of readmissions were considered secondary outcome measures. The mortality variables were assessed independently

Figure 1. Frequencies of noradrenaline administration, mechanical ventilation, and troponin levels during hospitalization by COVID categories

COVID = coronavirus disease 2019

**one-way ANOVA, ***linear-by-linear association

[A] Troponin levels, medians and 95% confidence intervals



[B] Data were presented separately for each group by COVID categories

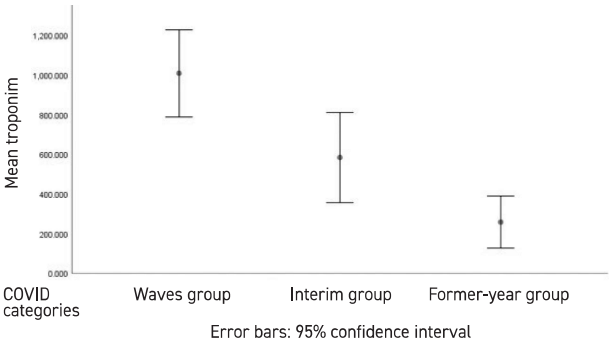


Table 1. Basic characteristics, clinical, and treatment data of the study population

	Total (n=6796)§	Waves group (n=2258)	Interim group (n=873)	Former-year group (n=2923)	*P*-value
Demographic and background characteristics					
Sex, n (%)					
Male	3538 (52.1%)	1175 (52%)	446 (51.1%)	1523 (52.1%)	0.863*
Female	3258 (47.9%)	1083 (48%)	427 (48.9%)	1400 (47.9%)	
Age in years, mean ± SD	76.6 ± 14.3	76.4 ± 14.8	75.8 ± 14.5	76.9 ± 13.9	0.103**
Charlson Comorbidity Index	Mild (1–2)	445 (6.5%)	171 (7.6%)	68 (7.8%)	
	Moderate (3–4)	1861 (27.4%)	673 (29.8%)	256 (29.3%)	**< 0.001***
	Severe (≥ 5)	3233 (47.6%)	939 (41.6%)	396 (45.5%)	
Interventions during hospitalization					
Mechanical ventilation (n, %)	613 (9%)	237 (10.5%)	71 (8.1%)	225 (7.7%)	**0.002***
Noradrenaline (n, %)	794 (11.7%)	339 (15%)	97 (11.1%)	258 (8.8%)	**< 0.001***
Emergency PCI (n, %)	33 (0.5%)	9 (0.4%)	2 (0.2%)	19 (0.7%)	0.182***
Vital signs in admission					
Systolic blood pressure (mmHg)	129.7 ± 28.1	127.5 ± 28	130.1 ± 27.4	131.1 ± 27.9	**< 0.001****
O_2 saturation (%)	94.9 ± 91.6	93.3 ± 9.8	94.3 ± 7.3	96.5 ± 137.8	0.485**
Heart rate (bpm)	86.1 ± 19.1	86.7 ± 19.1	86.7 ± 19.9	85.3 ± 18.8	**0.021****
Temperature (°C)	36.8 ± 0.9	36.7 ± 0.8	36.8 ± 1.1	36.8 ± 0.8	0.064**
Laboratory findings during admission (average)					
Hemoglobin (g/dl)	10.8 ± 2	10.6 ± 2.1	10.9 ± 2.1	10.9 ± 1.9	**< 0.001****
Leukocyte count (10^3/µl)	10.7 ± 10	11 ± 10.8	10.9 ± 7.6	10.3 ± 9.8	0.070**
Platelet count (10^3/µl)	225.4 ± 118.5	224.1 ± 126.3	226.3 ± 119.4	226.4 ± 113.7	0.807**
Creatinine (mg/dl)	1.5 ± 1.4	1.6 ± 1.5	1.4 ± 1.2	1.5 ± 1.4	**0.007****
CRP (mg/L)	102.2 ± 91.2	116.7 ± 96.4	101.4 ± 91.9	90.4 ± 84.3	**< 0.001****
Procalcitonin ng/ml)	12.7 ± 41.2	14.5 ± 46.7	22.9 ± 61.1	3.5 ± 10.5	0.139**
Uric acid (mg/dl)	6.9 ± 3.1	7.1 ± 3.3	6.7 ± 2.8	6.8 ± 2.9	**0.009****
Albumin (g/dl)	3.1 ± 0.6	3 ± 0.6	3.1 ± 0.6	3.1 ± 0.6	**< 0.001****
Alkaline phosphate (IU/L)	154.4 ± 207.5	162.2 ± 224	155.2 ± 196.7	149.6 ± 203.6	0.137**
Bilirubin (mg/dl)	1 ± 1.7	1.1 ± 1.7	1 ± 1.5	1 ± 1.8	0.113**
AST (IU/L)	66.6 ± 270.3	82 ± 340.7	60.5 ± 154.3	56.7 ± 253.1	**0.008****
ALT (IU/L)	45.3 ± 159.6	51.1 ± 183.2	44.3 ± 113.5	39.2 ± 140.4	**0.037****
GGT (IU/L)	145.6 ± 307.9	170.9 ± 353.4	157.2 ± 326.8	124.3 ± 245.2	**< 0.001****
LDH (IU/L)	407.3 ± 607.5	467.1 ± 682.7	419.2 ± 613.5	357.2 ± 490.2	**< 0.001****
Protein (g/dl)	6.1 ± 0.9	5.9 ± 0.8	6 ± 0.8	6.1 ± 0.8	**< 0.001****
Fibrinogen (mg/dl)	441.2 ± 212.6	447.2 ± 225.7	467.8 ± 220.4	420.8 ± 193.1	0.213**
INR	1.3 ± 0.8	1.3 ± 0.9	1.3 ± 0.5	1.3 ± 0.7	0.411**
D-dimer (ng/ml)	6005.9 ± 12,768.2	7078.8 ± 13,252.1	9710.6 ± 20,657.3	3505 ± 7276.1	**< 0.001****
Total cholesterol (mg/dl)	143.5 ± 51.6	140.1 ± 53.1	138.4 ± 36.4	145.6 ± 50.2	0.273**
Sodium (mEq/L)	139.3 ± 5.9	139.1 ± 6.2	139.2 ± 6.2	139.5 ± 5.5	0.051**
Potassium (mEq/L)	4.2 ± 0.6	4.2 ± 0.7	4.2 ± 0.6	4.2 ± 0.6	0.314**
Troponin (ng/L)	643.9 ± 2,294.5	1006.9 ± 2866.4	582.7 ± 1818.6	257.7 ± 1528.3	**< 0.001****

*chi-square test, **one-way ANOVA, ***linear-by-linear association

BPM = beats per minute, ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, GGT = gamma-glutamyl transferase, INR = international normalized ratio, LDH = lactate dehydrogenase, PCI = percutaneous coronary intervention, SD = standard deviation

§742 patients were excluded from further analysis after group stratification due to ambiguous admission dates

Table 2. Clinical outcomes of the study population

	Total (n=6796)§	Waves group (n=2258)	Interim group (n=873)	Former-year group (n=2923)	*P*-value
Mortality during hospitalization, n (%)	2135 (31.4%)	935 (41.4%)	266 (30.5%)	702 (24%)	**< 0.001***
30-day mortality from discharge, n (%)	1095 (16.1%)	439 (19.4%)	156 (17.9%)	377 (12.9%)	**< 0.001***
1-year mortality from discharge, n (%)	2279 (33.5%)	733 (32.5%)	341 (39.1%)	976 (33.4%)	**0.002***
Readmission in 1 month, n (%)	1628 (24%)	527 (23.3%)	222 (25.4%)	715 (24.5%)	**0.419***
Readmission in 1 year, n (%)	1886 (27.8%)	484 (21.4%)	254 (29.1%)	958 (32.8%)	**< 0.001***
Total readmissions count, median (IQR)	1 (0–2)	0 (0–2)	1 (0–2)	1 (0–3)	**< 0.001****

*chi-square test, **Kruskal-Wallis test

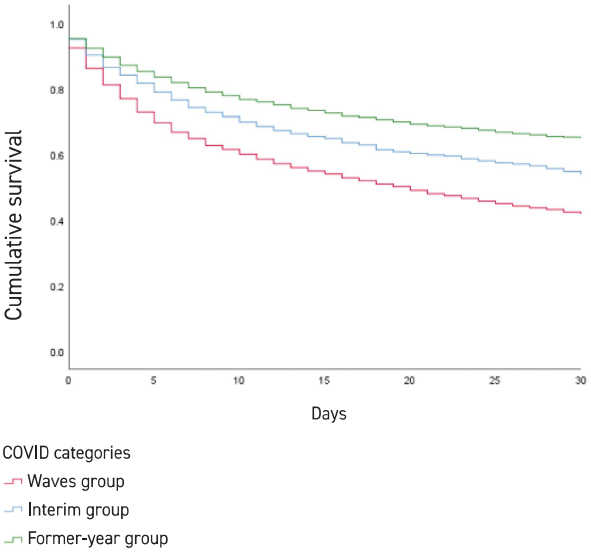
IQR = interquartile range

Bold signifies statistical significance

§742 patients were excluded from further analysis after group stratification due to ambiguous admission dates

Figure 2. Kaplan-Meier univariate survival analysis of 30-day mortality by COVID categories: noradrenaline administration, mechanical ventilation, and troponin levels during hospitalization by COVID categories

COVID = coronavirus disease 2019



without cumulative consideration. For normally distributed continuous variables, descriptive statistics were reported as mean ± standard deviation. Non-normally distributed continuous variables were presented as median (interquartile ranges). Statistical analysis of quantitative variables involved the utilization of appropriate tests such as the one-way ANOVA test and the Kruskal-Wallis test based on the distributional characteristics of the data. Categorical variables were summarized using frequencies, counts, and percentages. Their association was evaluated through the application of the chi-square test and linear-by-linear association when applicable. Furthermore, univariate survival analysis was performed using the Kaplan-Meier plot and the log-rank test, with 30-day mortality as the dependent variable of interest.

To obtain a thorough characterization of the study population, we analyzed the discharge diagnoses of the sample patients from their first admission. Due to the diverse nature of the data, which encompassed free-text descriptions and various International Classification of Diseases (ICD-9) codes [15], we employed a keyword-based classification approach. This approach involved creating 13 distinct diagnostic categories based on the affected physiological system (e.g., cardiovascular, respiratory, neurology) and metabolic disorders (e.g., hypertension, dyslipidemia, obesity). We also included a category for general deterioration, which encompassed patients with discharge diagnoses indicating a chronic condition or recent decline in general health status (e.g., anorexia, general deterioration, feeding difficulties). For patients who did not fit into any predefined categories based on our keyword criteria, we included a category of *other*. The COVID category included patients who were diagnosed with COVID during their hospitalization. A comprehensive list of specific keywords used for each diagnostic category can be found in Supplemental Table B (available in the online version only).

RESULTS

STUDY POPULATION CHARACTERISTICS

The study population is described in Table 1. There were no statistically significant differences observed in terms of age and gender between the groups. However, a significant disparity was identified in the Charlson Comorbidity Index [14] ($P < 0.001$). Notably, the waves group exhibited significantly higher rates of mechanical ventilation and noradrenaline administration (10.5%, $P = 0.002$ and 15%, $P < 0.001$, respectively). Moreover, patients in the waves group were more prone to liver function abnormalities. The interim group demonstrated elevat-

ed D-dimer levels ($P < 0.001$). Electrolyte levels did not differ significantly among the groups, except for phosphorus levels, which were slightly elevated in the waves group ($P < 0.001$). Troponin levels were notably higher in the waves group, with an average value of 1006.9 ng/L ± 2866.4 compared to 582.7 ± 1818.6 and 257.7 ± 1528.3 in the other groups ($P < 0.001$). A graphical representation of the prevalence of mechanical ventilation, noradrenaline administration, and troponin levels across all three groups is provided in Figure 1.

CLINICAL OUTCOME OF THE STUDY POPULATION: MORTALITY AND READMISSIONS

Significant disparities were identified among the groups in terms of mortality outcomes, including mortality during hospitalization, 30-day mortality, and 1-year mortality. The waves group exhibited higher mortality rates during hospitalization and within the first 30 days of presentation compared to the other groups (41.4% vs. 30.5% and 24%, $P < 0.001$, 19.4% vs. 17.9% and 12.9%, $P < 0.001$). In addition, the interim group demonstrated a slightly higher 1-year mortality rate compared to the other two (39.1 % vs. 32.5% and 33.4%, $P = 0.002$). Regarding readmission measures, no significant difference was found within the first 30 days, with approximately 24% in all groups ($P = 0.419$). However, significant variations were observed in the readmission rate at 1 year (21.4% in the waves group, 29.1% in the interim group, and 32.8% in the former-year group) and the total number of readmissions (median value of 0 in the waves group and 1 in the other two groups, $P < 0.001$ for both). Detailed clinical outcomes are shown in Table 2.

The survival analysis to examine the 30-day mortality among the groups revealed a statistically significant difference, as indicated by the log-rank test ($P < 0.001$). The survival rate in the waves group was consistently lower throughout the entire follow-up period. A visual representation of the analysis using the Kaplan-Meier method is provided in Figure 2.

PREDICTED 10-YEAR SURVIVAL BY CHARLSON COMORBIDITY INDEX

Considering the significant disparity in the scores across all groups, a detailed analysis of all variables utilized in the score was conducted. Patients with severe co-morbidities were more prevalent in the former-year group (53%) compared to the waves group (41.6%) and the interim group (45.5%) ($P < 0.001$). The findings of this analysis are presented in Supplemental Table C (available in the online version only). Providing a comprehensive insight into the examined variables.

DISCHARGE DIAGNOSIS CATEGORIES BY COVID CATEGORIES

A statistically significant difference was found in the distribution of discharge diagnosis categories among the study groups ($P < 0.001$). Most categories were more prevalent in the former-year group, while renal complications and malignancies were more common in the interim group. Hematologic complications, such as anemia and bleeding, were more prevalent in the waves group. Interestingly, the general deterioration category exhibited a higher prevalence in both the waves and the interim group compared to the former-year group (5.5% and 5.2% vs. 3.9%). Although COVID diagnosis at admission was an exclusion criterion, three patients were diagnosed with COVID infection during their hospitalization, all of whom were in the waves group. The prevalence of all categories in the three groups can be found in Supplemental Table D and Supplemental Figure 1 (both available in the online version only).

DISCUSSION

The main objective of this study was to examine the effects of the COVID-19 pandemic on the clinical outcomes of patients admitted to non-COVID internal medicine wards. We hypothesized that the COVID-19 pandemic would have a detrimental effect on the outcomes of hospitalized patients.

The study was designed to characterize the differences in hospitalized patients during the interim periods between the waves as well as during and before the COVID-19 pandemic. Specifically, the focus was on examining the prevalence of critically ill patients with hemodynamic and/or respiratory failure who required treatment with noradrenaline and mechanical ventilation. In addition, we investigated all-cause mortality and readmissions as outcome measures. To address potential confounding factors related to season-dependent fluctuations in mortality, particularly due to other viral outbreaks coinciding with the COVID-19 pandemic, each period was compared to the corresponding period in the previous year. Although our research was conducted at a single center, Sheba Medical Center is the largest tertiary referral center in Israel, thus providing a representative sample of the Israeli population.

Our findings indicated that non-COVID patients admitted to the internal medicine departments during the COVID pandemic exhibited elevated mortality rates during hospitalization and 1-year follow-up. These patients were also more likely to present with critical illness. The prevalence of these primary outcomes was notably higher during the peak periods of the pandemic compared to the nadirs. Both the waves and interim groups demonstrated significantly higher short-term (1-month) and long-term (1-year) mortality compared to the corresponding periods in the preceding year. We focused on deceased patients, and thus we analyzed the timing and comparison of death among the three groups rather than mortality rates. Moreover, the waves group exhibited a higher prevalence of re-hospitalizations in the long term and a greater number of readmissions. The only clinical outcome that did not differ significantly among the three groups was readmission within 1 month, and we propose that this finding may be partially attributed to the high short-term mortality in the

waves group. Prior studies conducted in the United States reported increased mortality rates during the COVID pandemic, mainly associated with heightened healthcare system demands [16,17]. However, these studies primarily focused on COVID patients and their associated co-morbidities. In contrast, we focused predominantly on non-COVID patients during the pandemic waves who constituted most hospitalized individuals in Israel throughout the pandemic.

Previous studies posited that the adverse outcomes observed in hospitalized patients during the COVID-19 pandemic could be linked to delayed medical assistance resulting in patients presenting at hospitals in advanced stages of their concurrent illness [12,13,18,19]. Our study extended previous results and provided supporting evidence by revealing worse clinical and laboratory parameters on admission including anemia, acute kidney injury, liver enzyme abnormalities, and elevated troponin levels in the waves group compared to the two reference groups. The documentation of discharge diagnoses in medical records also demonstrated a higher prevalence of diagnoses associated with general deterioration in the waves group. Collectively, these findings suggest that non-COVID patients experienced more severe and complicated hospitalizations during the pandemic, particularly during the peaks.

Building on these findings, we conducted Charlson Comorbidity Index and discharge diagnosis analyses. Our objective was to elucidate whether the increased mortality and severity of illnesses were attributed to the patient's clinical characteristics rather than indicative of a burdened healthcare system and resource depletion. The Charlson Comorbidity Index is a validated score that serves as a reliable predictor of survival and provides insights into patient co-morbidities. Our analysis revealed a higher proportion of patients with severe co-morbidities in the former-year group compared to the waves group and the interim group. Further examination of individual variables included in the score, such as myocardial infarction, heart failure, and cerebrovascular accidents, indicated even higher rates in the former-year group. This result suggests that the proper outcome observed in the waves group cannot be solely attributed to co-morbidities, as they had a comparatively better than expected survival. Our findings support the hypothesis that the main driver behind the worsened outcomes of non-COVID patients during the pandemic was the strain on the healthcare system and the depletion of resources. Given the absence of prolonged and significant shortage in equipment, beds, and medications, we propose that the scarcity and exhaustion of the medical personnel during the pandemic likely played a pivotal role in the described outcomes.

While the study benefited from a large sample size and robust data collection methods, limitations exist regarding the scope of outcomes examined and the generalizability of findings. However, the data are considered reliable since they were obtained directly from patients' electronic medical records. We focused on deceased patients, and thus did not address overall mortality rates. Although we conducted a single-center study, it was conducted in a major referral center for patients across Israel, enhancing the generalizability of the findings. The study lacks direct measures of the shortage of medical staff, although it was suggested as a possible contributing factor to the observed outcomes. Future research should address these limitations to gain a more comprehensive understanding of the implications of a pandemic on hospitalized patients. Future studies should consider incorporating measures of healthcare recourse availability and staffing levels.

CONCLUSIONS

This retrospective observational cohort study provides insights into the implications of the COVID pandemic on the outcomes of non-COVID patients admitted to internal medicine departments. The pandemic affected not only COVID patients but the entire medical system. Hospitalized non-COVID patients experienced worsened outcomes during the waves of the pandemic compared to the interim periods and the previous year. We attribute this phenomenon primarily to the strain on resources, particularly the availability of medical personnel. These findings underscore the importance of preparedness for large-scale threats and the implementation of effective resource allocation policies and strategies.

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Capsule

A vertebral skeletal stem cell lineage driving metastasis

Vertebral bone is subject to a distinct set of disease processes from long bones, including a much higher rate of solid tumour metastases. The basis for this distinct biology of vertebral bone has so far remained unknown. **Sun** et al. identified a vertebral skeletal stem cell (vSSC) that co-expresses ZIC1 and PAX1 together with additional cell surface markers. vSSCs display formal evidence of stemness, including self-renewal, label retention and sitting at the apex of their differentiation hierarchy. vSSCs are physiologic mediators of vertebral bone formation, as genetic blockade of the ability of vSSCs to generate osteoblasts results in defects in the vertebral neural arch and body. Human counterparts of vSSCs can be identified in vertebral endplate specimens and display a conserved differentiation hierarchy and stemness features. Multiple lines of evidence indicate that vSSCs contribute to the high rates of vertebral metastatic tropism observed in breast cancer, owing in part to increased secretion of the novel metastatic trophic factor MFGE8. The results indicated that vSSCs were distinct from other skeletal stem cells and mediated the unique physiology and pathology of vertebrae, including contributing to the high rate of vertebral metastasis.

Nature 2023; 621: 602

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Capsule

Neutralization, effector function, and immune imprinting of Omicron variants

Currently circulating SARS-CoV-2 variants have acquired convergent mutations at hot spots in the receptor-binding domain1 (RBD) of the spike protein. The effects of these mutations on viral infection and transmission and the efficacy of vaccines and therapies is poorly understood. **Addeita** and colleagues demonstrated that recently emerged BQ.1.1 and XBB.1.5 variants bind host ACE2 with high affinity and promote membrane fusion more efficiently than earlier Omicron variants. Structures of the BQ.1.1, XBB.1 and BN.1 RBDs bound to the fragment antigen-binding region of the S309 antibody (the parent antibody for sotrovimab) and human ACE2 explain the preservation of antibody binding through conformational selection, altered ACE2 recognition and immune evasion. The authors showed that sotrovimab binds avidly to all Omicron variants, promotes Fc-dependent effector functions, and protects mice challenged with BQ.1.1 and hamsters challenged with XBB.1.5. Vaccine-elicited human plasma antibodies cross-react with and trigger effector functions against current Omicron variants, despite a reduced neutralizing activity. This reaction suggests a mechanism of protection against disease exemplified by S309. Cross-reactive RBD-directed human memory B cells remained dominant even after two exposures to Omicron spikes, underscoring the role of persistent immune imprinting.

Nature 2023; 621: 592

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