Comparing Covid-19 pandemic waves in hospitalized patients – a retrospective, multicenter, cohort study

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Summary – This is an Israeli cohort study of hospitalized Covid-19 patients during the first 3 waves of the pandemic. Invasive ventilation and mortality rate were 1.5 to 2 times higher during the 3rd wave than during the 1st and 2nd waves.

ABSTRACT

BACKGROUND

Covid-19 disease was first diagnosed in Israel at the end of February 2020. Until the end of June 2021 842,536 confirmed cases and 6428 deaths were accumulated. The aim of our multicenter retrospective cohort study is to describe the demographic and clinical characteristics of hospitalized patients and to compare the pandemic waves before immunization.

METHODS

Out of 22302 patients hospitalized in general medical centers we randomly selected 6329 admissions for the study. Of these, 3582 and 1106 were eligible for the study in the first period (1st & 2nd waves), and in the second period (3rd wave), respectively.

RESULTS

Thirty-day mortality was higher in the 2nd period than in the 1st period, 25.20% versus 13.68% (P<0.001). Invasive mechanical ventilation supported 9.19% and 14.21% of the patients in the 1st period and 2nd period, respectively. Extracorporeal Membrane Oxygenation (ECMO) was used more than twice as often on the 2nd period .

CONCLUSIONS

Invasive ventilation, use of ECMO and mortality rate were 1.5 to 2 times higher on the 2nd period than in the 1st period. Patients of the 2nd period had a more severe presentation and higher mortality than those of the 1st period.

KEY WORDS: corona, SARS-CoV-2, Covid-19, cohort study, pandemic

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-SoV-2) that causes coronavirus disease 2019 (Covid-19) was first diagnosed in Israel at the end of February 2020. Since then and up to June 2021 there were 842536 confirmed Covid-19 cases and 6428 deaths[1]. Three waves of the pandemic were clearly defined in Israel; each subsided following social distancing, use of masks, isolation of corona cases, and finally strict lock down[2].

The Israel Ministry of Health has approved both mRNA-based vaccines (Moderna/NIH and Pfizer/BioNTech), and national immunization program has started vigorously on December 19, 2020 (with the Pfizer/BioNTech vaccines, mRNA-BNT162b2, which require 2 doses). The national immunization program prioritized elderly adults and other populations with higher risk for severe COVID-19 followed by the general population. On July 3, 2021 5174406 Israelis, (55.64% of the total Israeli population) were immunized with 2 injections of BNT162b2 RNA vaccine of Pfizer. High efficiency of prevention of disease, symptoms, hospitalization and severe illness was reported in Israel, with 92%, 94%, 87% and 92% rates, respectively[3].

Reports from China, Italy, Great Britain and the USA at the beginning of the first wave suggested high morbidity, mortality, stressed hospitals, and intensive care units utilization[4]. When 500 new cases were diagnosed in Israel, a tight lock down of 32 days was issued and the 1st wave resulted in 4000 hospitalizations and 329 deaths[5]. The second and third waves were severe and ended with 40000 hospitalizations and 6099 more deaths[6].

The epidemiological and clinical presentations were definitely changed with the successful immunization project. The aim of our multicenter report is to describe the demographic and clinical characteristics, underlying diseases, laboratory findings and outcomes among hospitalized non-immunized patients with Covid-19 in Israel, using in-

depth record of about 25% of hospitalized patients, creating a valid and representative retrospective nation-wide cohort, and to compare the 2 periods of the pandemic.

METHODS

STUDY POPULATION, SETTING AND DATA COLLECTION

Between February 28th 2020 and November 5th 2020, 19308 Covid-19 patients were hospitalized in 24 out of 30 general medical centers of Israel. We randomly selected about 25% of patients in each hospital resulting in 4697 admissions; of these, 3582 non-immunized patients were eligible for the study in the 1st & 2nd waves (period I). Between November 6th 2020 to January 15th 2021 (part of the 3rd wave, period II, representing more than 50% of the patients in the 3rd wave), 2994 Covid-19 patients were hospitalized in 6 general medical centers, of these we randomly selected 1632, and 1106 non-immunized patients were eligible for the study.

The original SARS-CoV-2 virus characterized the 1st period and the British variant the 2nd period. We excluded patients who had been admitted for any reason other than Covid-19, and diagnosed as positive for Covid-19 after hospitalization. Only confirmed cases of Covid-19, defined by a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected from a nasopharyngeal swab, were included.

A team of experienced nurses collected the data from the electronic patients' files in every hospital. Sixty-one parameters were computed for each patient: Demographic parameters: date of performing RT-PCR for SARS-CoV-2 virus, date of admission, date of discharge or death, name of medical center, department, age, gender. Underlying Diagnoses: diabetes mellitus, arterial hypertension, hyperlipidemia, cardiac disease, lung disease, kidney disease,

smoking, obesity (BMI>30), active malignancy, immune deficiency. Clinical symptoms: clinical status (easy, medium, severe), fever of 38^0 or higher, cough, dyspnea, headache, diarrhea, vomiting, abdominal pains, fatigue, muscle pains, taste and smell changes. Most extreme vital signs and pathological laboratory findings on admission: oxygen saturation, blood pressure, hemoglobin, leukocytes, lymphocytes, albumin, calcium, glucose, sodium, potassium, blood urea nitrogen (BUN), creatinine, D-dimer. Respiratory support and oxygen treatment: oxygen mask, high flow oxygen by nasal cannula, non-invasive ventilation, invasive ventilation, extra corporal membrane oxygenation (ECMO), prone positive ventilation, nitric oxide (NO), hemodialysis. Treatment: steroids, remdesivir, convalescent plasma, vitamin D, enoxaparin. Outcomes: 30 days mortality, in-hospital mortality, discharge with or without oxygen support. Duration of hospitalization was computed for each parameter and compared.

STUDY DEFINITIONS

Patients' data were censored and anonymized at the time of collection. Acute respiratory distress syndrome (ARDS) was defined when oxygen saturation was less than 93%, more than 30 breaths per minute and bilateral pulmonary infiltrates on chest imaging. Age distribution was plotted against duration of hospitalization, frequency of invasive ventilation and mortality. The duration of time between RT-PCR test for SARS-CoV-2 virus and the day of hospitalization was recorded for every patient in both periods. The case fatality rate per hospital per period was defined as the percentage of patients admitted for Covid-19 who died in that hospital during that period. The range of case-fatality rates (CFRs) was 6.7% - 19.9% with a median of 13.0%. A low level of CFRs was considered to be 6.7% - 13.0%, and a high level 13.4% - 19.9%.

STASTISTICAL ANALYSIS

Descriptive statistics were used when reporting the data. Results are presented as means and standard deviations. Analysis was performed with Statistical Analysis System (SAS) software.

Data of the 1st period (1st and 2nd waves combined) was compared with data of the 2nd period (3rd wave). We performed multivariate analysis to correlate background diseases with invasive ventilation and mortality. Logistic regression models were used for invasive ventilation and mortality, controlling for underlying diagnoses and demographics, with comparison between the two periods. We also compared hospitals, which had low mortality rate, with those with high mortality rate in both periods, looking for possible explanation for the differences in background diseases and their number per patient, symptoms at admission, pathological results of laboratory tests and treatments.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

The clinical status was severe in 19.35% of the patients in the 1st period and 35.91% in the 2nd period. Patients were older on the 2nd period than in the 1st period, 71.01% and 58.23% were older than 60 years, respectively (Table 1). Patients admitted during the 2nd period were more likely to be male and had a higher prevalence of all underlying diseases except for active smoking (Table 1). Fever of 38^0C or higher and dyspnea on admission were found in 28.84% and 46.01%, 32.47% and 54.69% in the 1st period and the 2nd period, respectively.

In the 1st period 53% underwent RT-PCR testing for SARS-CoV-2 virus within 24h of admission, and 84% within 7 days before admission. The respective data for the 2nd period

were 52% and 83%. Thus, duration of disease before admission could not explain the difference.

Hospital length of stay directly related with severity of illness and need for mechanical ventilation, and was similar in all waves (Table 1)

LABORATORY FINDINGS

Laboratory tests results on patients' admission were more likely to be pathological during the 2nd period than during the 1st period, except for the rate of hypokalemia (Table 1). Hypoxia, anemia, hypoalbuminemia and elevated D-dimer levels were presented in 10% more patients in the 2nd period than in the 1st period.

MICROBIOLOGY RESULTS

RT-PCR testing was performed on every admitted patient, and gene sequencing was done whenever needed according to epidemiological information. On the 1st period all the patients had the original virus imported from China and Europe. This variant changed to the British variant that expanded to 80% of patients on the 2nd period.

DRUG THERAPY

Patients were treated with steroids, remdesivir, convalescent plasma, vitamin D and anticoagulants in both periods (Table 1). Therapeutic use of anticoagulants, steroids and vitamin D was higher in the 2nd period than the 1st period, 79.79%, 75.69%, 20.96%, versus 66.19%, 48.99%, 13.87% of the cases, respectively.

Half of the patients on high flow oxygen or invasive ventilation received remdesivir. Remdesivir was associated with reduced mortality in these patients with an estimated OR of 0.53 for mortality (P=0.0013). The inverse association between remdesivir treatment and

mortality was seen in both the 1st and 2nd periods, which comprise patient populations that are quite different in several aspects, including the latter period having more elderly and more severely ill patients. However, within the group of those receiving high flow oxygen and invasive ventilation, the pattern of remdesivir prescription was opposite to that expected. Those with better prognosis were more likely to receive remdesivir: in the 1st period the percentage of patients receiving remdesivir among those older than 70 years and those with heart disease, lung disease, kidney disease and active malignancy versus patients younger than 70 years and those without these diseases, were 39%, 38%, 41%, 25%, and 39%, versus 61%, 57%, 51%, 55%, and 50%, respectively. Similar results were found in the 2nd period – 16%, 13%, 11%, 8%, and 11% versus 30%, 28%, 26%, 27% and 24%, respectively. Similarly, in the 1st period, the percentage of patients on high flow oxygen or invasive ventilation receiving remdesivir among those with low blood pressure, anemia, leukocytosis and high creatinine level was 26%, 41%, 39% and 32% versus 50%, 56%, 53% and 61% among those without these conditions, respectively; and in the 2nd period, these percentages were 12%, 11%, 18%, and 10% versus 23%, 34%, 24%, and 29%, respectively.

RESPIRATORY SUPPORT AND MECHANICAL VENTILATION

Half of the patients in the 1st period needed oxygen therapy in comparison with 2/3 of the patients in the 2nd period . High flow oxygen by nasal cannula was given to 19.16% and 31.90% of patients in the 1st period and 2nd period, respectively. Invasive mechanical ventilation supported 9.19% and 14.21% of the patients in the 1st period and 2nd period, respectively. Nitric oxide inhalation and prone positioning were similarly practiced in both periods. ECMO was used more than twice as often on the 2nd period (Table 1).

A logistic regression model for invasive ventilation which includes age, gender, patient's status on admission and underlying diseases demonstrated a higher rate of invasive

ventilation for patients with heart and lung diseases in the 1st period (OR 1.494, p = 0.0069, OR 1.436, p = 0.0385, respectively), and in patients with diabetes mellitus (OR 1.866, p = 0.0023) and kidney diseases (OR 1.763, p = 0.0183) on the 2nd period (Table 2). A positive correlation was found between the need for invasive ventilation and the number of background diseases per patients in both periods (Figure 1, Figure 2).

OUTCOMES

In hospital mortality and 30-day mortality were significantly higher on the 2nd period than on the 1st period (Table 1). A logistic regression model for 30-day mortality which includes age, gender, patient's status on admission and underlying diseases demonstrated higher mortality rates for patients with heart disease, kidney disease and immune suppression on the 1st period (OR 1.987, p < 0.0001, OR 1.590, p=0.0013, OR 2.552, p = 0.0016, respectively), and in patients with diabetes mellitus, heart diseases, kidney diseases, and active malignancy in the 2nd period (OR 1.678, p = 0.0043, OR 1.513, p = 0.0231, OR 1.995, p = 0.001, OR 2.849, p = 0.0039, respectively) (Table 2). A positive correlation was found between 30-day mortality and the number of background diseases per patient in both periods (Figure 1, Figure 2, Table 2, and Table 3).

Case-fatality rates were higher in some hospitals more than in others, where patients were older, had worse laboratory tests results, and with more background diseases (Table 3). This was found in both periods.

DISCUSSION

We describe a cohort of 4688 Covid-19 Israeli patients, hospitalized between February 28th 2020 and January 15th 2021, comparing 2 periods of the Covid-19 pandemic. Invasive ventilation, use of ECMO and mortality rate were 1.5 to 2 times higher on the 2nd period than

in the 1st period. Since no breakthrough in patients' management happened, severe outcome was probably correlated with male gender, a worse clinical presentation (fever and dyspnea), more background diseases, poorer results of laboratory tests on admission, and higher prevalence of the British variant, which was present in 90% of the patients on the 2nd period. This observation may also explain the higher use of certain drugs on the 2nd period, such as anticoagulants, steroids and vitamin D. The duration of disease before admission was similar in both periods and could not explain the difference in patient clinical status and outcome.

The range of mortality rates in different countries changed significantly between cohorts and correlated with the patients' age, gender, clinical status on admission and with the capabilities of the local health system (7-28). In our cohort, we had more men than women, and 38.45% - 51.92% were older than 70 years. The results from Israel resemble the experience in other countries showing that patients with coexisting conditions and older age are at higher risk for severe disease, invasive mechanical ventilation and poor outcome. Bhatraju PK et al reported a case-fatality rate of 50% in their series of patients admitted to the intensive care unit (7). Burn E et al described a cohort of 34128 adult patients hospitalized with Covid-19 in the USA, South Korea and Spain (8). In the USA the proportion of those who had diabetes mellitus was up to 43%, arterial hypertension up to 70%, heart disease up to 49%, and cancer up to 18%. Similar data were recently published from other countries (9-28).

The British (alpha variant, B.1.1.7) characterized our 3rd wave of the pandemic, was found to be 45% more contagious than the original virus (29). In January 2021 this variant was responsible for 90% of Covid-19 cases in Israel. A UK case-control study of 54906 patients between October 1st 2020 and January 29th 2021 reported that patients infected with the Alpha variant had a hazard ratio for death within 28 days of testing of 1.64 (95%CI 1.32-2.04), as compared with matched patients positive for other variants of SARS-CoV-2 (30).

Similar finding were found by others (31). Thus, the British variant may explain the high mortality rates of the Israeli patients in the 2nd period.

Our study has limitations, being retrospective and descriptive, and not including all the admitted patients. However, our cohort was composed of hospitalized patients in referral, tertiary, and academic centers as well as smaller rural, district hospitals, and we expect it was representative of the national experience. It seems that, within the group of more seriously ill patients there was a tendency to prescribe remdesivir to those patients with a better prognosis. Thus, if we did a straight analysis of remdesivir versus no remdesivir with no statistical adjustment, we would not be surprised to see that patients receiving remdesivir have lower mortality. However, even after statistical adjustment for prognostic factors, we found a survival advantage to those receiving remdesivir. It would therefore be tempting to conclude that remdesivir does reduced the risk of death in patients receiving high flow oxygen or invasive ventilation. However, it is well known that statistical adjustment for prognostic factors usually does not completely remove the biases caused by selection, and the observed benefit to the remdesivir patients could easily be due to residual confounding, i.e. incomplete adjustment for the prescribing pattern.

In conclusion, we describe the three waves of Covid-19 pandemic in Israel. Patients' clinical status on admission, fever, dyspnea, background diseases and pathological laboratory results may be predictors for invasive mechanical ventilation and for mortality. The patients of the 3rd wave (second period) had a more severe presentation and higher mortality than the 1st & 2nd waves (first period).

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Figure legend

Figure 1. Correlation between the number of background diseases, invasive ventilation and 30-day mortality. Figure 1a. 1st & 2nd waves (1st period). Figure 1b. 3rd wave (2nd period).

Figure 2. Logistic model includes invasive ventilation, 30-day mortality and background diseases. Figure 2a. 1st & 2nd waves (1st period). Figure 2b. 3rd wave (2nd period).

Table 1. Comparison between the 1st period (N=3582), and the 2nd period (N=1106).

	1st and 2nd Waves		3rd Wave	
Parameter	%	Duration of hospitalization, average, d	%	Duration of hospitalization, average, d
Age,y 0-49	26.75	4.63	15.93	6.04
50-59	15.02	7.80	13.06	9.10
60-69	19.78	10.31	19.09	9.88
70-79	18.67	11.08	21.60	11.27
80-89	14.58	9.87	20.84	8.79
+90	5.20	8.60	9.48	7.39
Gender Women	44.94	7.37	42.11	8.55
Gender Men	55.06	9.24	57.89	9.33
Clinical status - mild	63.06	7.04	49.69	8.87
Clinical status - moderate	17.59	9.53	14.4	6.40
Clinical status - severe	19.35	11.81	35.91	10.23
Diabetes Mellitus	33.74	11.03	39.54	10.53
Hyperlipidemia	38.22	10.24	44.91	9.51
Arterial Hypertension	47.07	10.44	57.10	10.18
Heart Disease	25.40	10.54	33.34	9.31
Lung Disease	12.28	10.84	15.58	9.30
Kidney Disease	13.35	11.25	16.89	10.94
Active Smoking	5.87	9.46	4.06	9.76
Obesity, BMI>30	19.86	9.62	23.19	11.21
Active Malignancy	4.21	10.46	6.90	9.47
Immune suppression	3.31	10.13	5.85	10.56
Fever>38	28.84	9.77	32.47	10.02
Cough	43.20	8.52	36.87	8.29
Dyspnea	46.01	8.79	54.69	9.64
Headache	8.16	5.82	4.37	7.05
Diarrhea	9.39	7.38	4.96	8.96
Vomiting	6.80	6.51	5.23	7.07
Abdominal Pain	5.94	6.52	3.54	7.77
Muscle Pain	11.55	6.28	6.08	5.64
Fatigue	42.41	8.51	34.68	8.63
Taste/Smell loss	6.01	6.22	3.77	6.19
High Blood Pressure	29.10	9.23	35.79	9.46
Low Blood Pressure	1.80	10.28	3.2	8.39
Low Saturation	24.47	11.34	36.88	10.83
Low Hemoglobin	34.17	10.75	44.79	9.80
Leukocytopenia	22.50	7.15	19.85	8.21
Leukocytosis	11.36	12.71	16.47	12.83
Hypoalbuminemia	25.49	12.71	35.62	11.90
Hypocalcemia	29.40	11.28	33.13	12.52
Hyponatremia	25.29	10.67	25.85	10.60
Hypokalemia	11.57	7.98	7.94	9.83
High Creatinine Level	21.57	11.18	26.06	11.03
High BUN	9.95	11.83	14.61	11.10
High d-dimer	28.47	11.37	41.99	10.69
In Hospital Mortality	12.87	13.78	21.17	13.48
30-day Mortality	13.68	9.42	25.20	9.40
Any ventilation	19.16	18.23	31.90	16.43
Invasive Ventilation	9.19	23.88	14.21	22.60
ECMO	0.83	38.20	1.50	33.02
Pronation	4.43	23.40	5.99	24.14
NO	3.34	27.60	5.17	26.89
CRRT	0.73	26.85	0.89	15.88
Dialysis	2.58	19.09	3.25	17.87
Steroids treatment	48.99	11.56	75.69	10.62
Remdesivir	18.26	14.13	14.87	13.76
Convalescent plasma	8.52	14.32	5.75	12.20
Vasopressors	9.08	20.61	13.67	22.04
Vitamin D	13.87	11.95	20.96	11.70
Anticoagulants	66.19	10.52	79.79	10.43

Table 2. Logistic regression model for invasive ventilation and 30-day mortality according to background diseases. Comparison between the 1st period (N=3582), and the 2nd period (N=1106).

	Invasive Ventilation				30-day Mortality			
	1st and 2nd Waves		3rd Wave		1st and 2nd Waves		3rd Wave	
	OR	P	OR	P	OR	P	OR	P
Female	0.403	<.0001	0.731	0.1039	0.816	0.1003	0.677	0.0271
Age 50-59 y	1.742		0.924		4.43		0.973	
Age 60-69 y	2.702		0.834		7.03		2.696	
Age 70-79 y	2.198	0.0008	1.158	0.0034	14.243	<.0001	4.421	<.0001
Age 80-89 y	1.758		0.449		27.203		9.139	
Age+90 y	1.14		0.216		68.52		17.542	
Status - medium	1.564	<.0001	0.952	0.0015	1.011	<.0001	0.6	<.0001
Status - severe	5.664		1.996		3.163		2.183	
Diabetes	1.193	0.2498	1.866	0.0023	1.157	0.2524	1.678	0.0043
Hyperlipidemia	1.098	0.5293	0.885	0.5895	0.89	0.3406	0.899	0.5703
Hypertension	1.22	0.239	1.16	0.5256	1.148	0.3387	0.976	0.9057
Heart disease	1.494	0.0069	0.961	0.8633	1.987	<.0001	1.513	0.0231
Lung disease	1.436	0.0385	1.295	0.2909	1.218	0.2038	1.341	0.165
Kidney disease	1.213	0.27	1.763	0.0183	1.59	0.0013	1.995	0.001
Smoking	1.207	0.432	1.826	0.1	1.356	0.1956	0.996	0.9914
Obesity	1.187	0.2806	1.304	0.2363	0.728	0.0446	1.047	0.8307
Active malignancy	1.095	0.775	1.695	0.1932	1.529	0.13	2.849	0.0039
Immune suppression	1.527	0.2191	0.572	0.2621	2.552	0.0016	1.579	0.3042

Table 3. Comparison between medical centers with low fatality rate of 6.7% -13.0%, and high fatality rate of 13.4% - 19.9% (%).

	1st period		2nd period	
	Hospitals with a low fatality rate	**Hospital with a high fatality rate**	**Hospitals with a low fatality rate**	**Hospital with a high fatality rate**
N	1862	1720	479	627
Age (year) mean+SD	59.17+20.38	63.22+19.63	64.34+21.93	70.74+16.84
median	62	66	67	73
0-69	65.14	57.84	53.19	40.82
70-100	34.86	42.16	46.81	59.18
Gender men	55.27	54.55	60.48	54.21
women	44.73	45.45	39.52	45.79
Background diseases				
Diabetes Mellitus	31.17	36.39	38.01	41.72
Hyperlipidemia	35.27	41.27	40.88	50.66
Arterial Hypertension	43.63	50.63	54.56	60.71
Heart disease	21.79	29.12	29.07	39.44
Lung disease	12.23	12.33	13.61	18.37
Kidney disease	12.02	14.71	16.43	17.55
Smoking	5.69	6.05	3.57	4.76
Obesity	18.37	21.40	23.16	23.23
Active Malignancy	4	4.42	6.75	7.12
Immune Suppression	3.66	2.95	5.09	6.93
Number of background diseases				
0-2	64.75	57.96	55.23	44.82
3+	35.25	42.04	44.77	55.18
Symptoms				
Fever 38^{0}C or higher	26.25	31.51	26.75	36.49
Laboratory Results				
Anemia	31.82	36.59	43.95	46.00
Hypoalbuminemia	17.21	34.03	30.10	43.48
High creatinine	20.06	23.14	25.15	27.36
High D-dimer	27.08	29.91	39.98	44.86
Treatments				
Steroids	48.25	49.75	74.16	77.86
Convalescent plasma	5.95	11.17	0.40	13.37
Vitamin D	11.44	16.38	14.56	30.09
Anticoagulants	64.34	68.10	78.55	81.55
ECMO	0.64	1.04	0.61	2.78

Figure 1

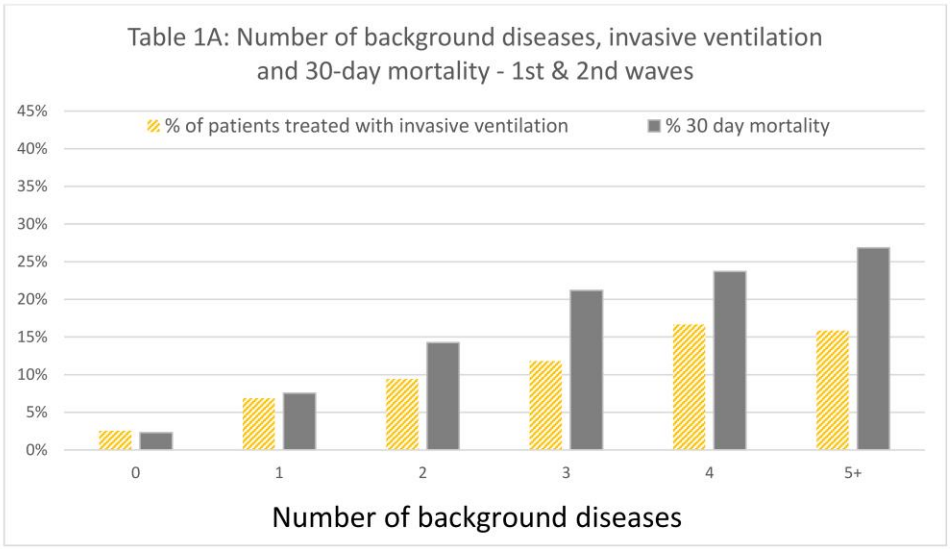


Table 1A: Number of background diseases, invasive ventilation and 30-day mortality - 1st & 2nd waves
% of patients treated with invasive ventilation
% 30 day mortality
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
1
2
3
4
5+
Number of background diseases

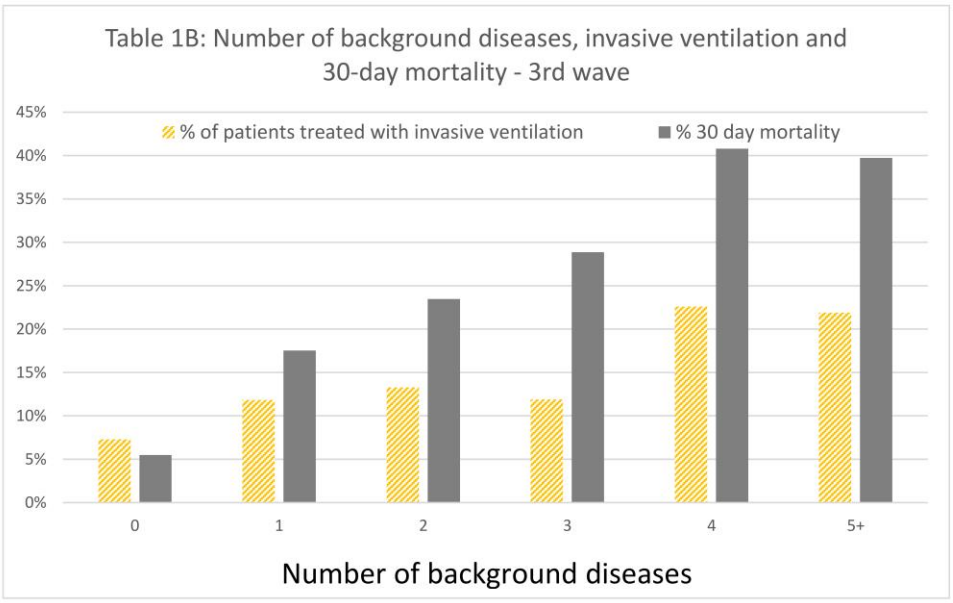
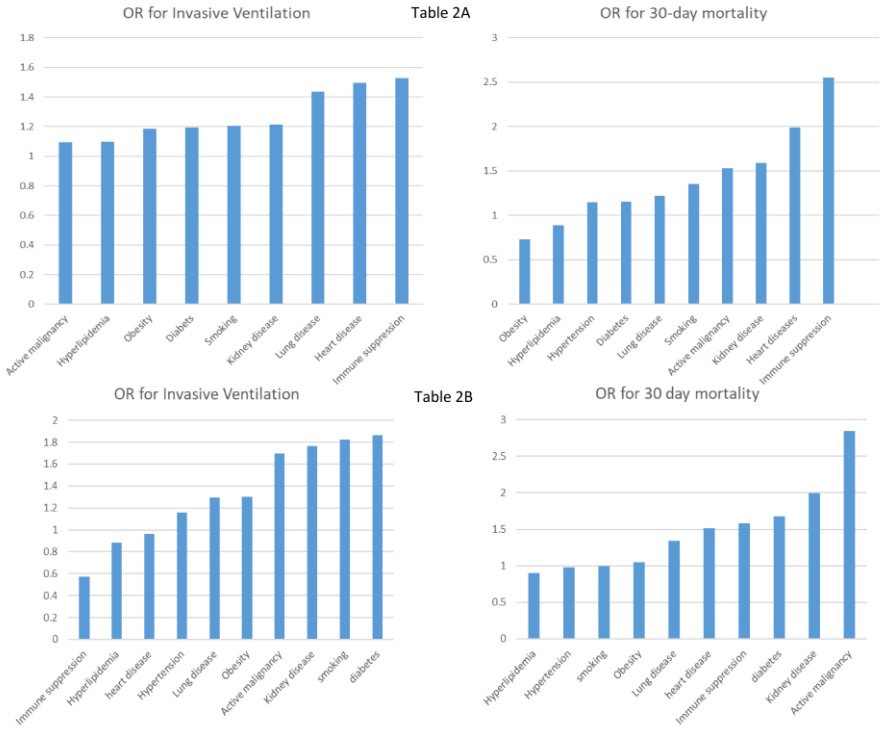


Table 1B: Number of background diseases, invasive ventilation and 30-day mortality - 3rd wave
% of patients treated with invasive ventilation
% 30 day mortality
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
1
2
3
4
5+
Number of background diseases

Figure 2


OR for Invasive Ventilation
Table 2A
OR for 30-day mortality
OR for Invasive Ventilation
Table 2B
OR for 30 day mortality