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Survival of elderly COVID-19 intensive care patients in the first and second Belgian wave: a retrospective single center analysis

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Abstract: Coronavirus disease 2019 emerged in China at the end of 2019 and rapidly spread throughout the rest of the world. In 2020, Belgium experienced two waves of COVID-19 infections. In the first wave (March, April and May 2020), scientific knowledge was very limited and therapy consisted of supportive care and experimental drugs like hydroxychloroquine, ritonavir/lopinavir and remdesivir. Although curative therapy was still lacking, there was a large increase in knowledge on COVID-19 by the time the second wave occurred (October, November, December 2020). The previously mentioned experimental drugs were no longer administered, dexamethasone became part of the standard therapy and prophylactic anticoagulation dosing was increased. The use of high flow nasal cannula was maximized and in case of mechanical ventilation, pressure-controlled ventilation was chosen.

In this analysis, characteristics and outcomes of elderly intensive care patients in one Belgian tertiary center during the first and second wave were compared, as a sub-analysis of the European COVIP trial (Corona Virus disease (COVID19) in Very Elderly Intensive care Patients (VIPs). A VIP network study). In the first and second wave, respectively 44 and 46 patients of 70 years and older with COVID-19 were admitted to the ICU in ZOL Genk. No significant differences were demonstrated in baseline characteristics between the first and second wave. Mean age (77 years in both waves) and disease severity (APACHE IV score 34 in the first wave and 33 in the second) were comparable. As for outcome, we found no difference in 90-day, 30-day and ICU survival. Twenty-three patients (52.27%) survived their first 90 days in the first wave, whereas 24 patients (52.17%) did so in the second wave. Median length of stay was not significantly different, 190 hours (7.92 days) in the first wave, 174 hours (7.25 days) in the second wave. The lack of improvement in survival during the second wave may be due to the already selective use of corticosteroids during the first wave, the only known drug to have some effect on patient outcome in COVID-19. The 90-day survival rate of elderly patients admitted to the ICU for COVID-19 was in line with the 52% of the European COVIP registry.

Keywords: COVID-19; SARS-CoV-2; critical care; elderly; aged.

Introduction

Coronavirus disease 2019 (COVID-19) is a new viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). The first patients were reported in December 2019 in Wuhan, China. Over the next weeks, the virus travelled around the world and started a new pandemic. In May 2021 more than 160 million cases and more than 3 million deaths were reported worldwide *(https://covid19.who.int/)*.

Although one fifth of patients remains asymptomatic throughout the course of the disease, most patients develop fever, cough and shortness of breath

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(1). Severe and critical cases occur in approximately 14% and 5% of patients, respectively. Critical cases include severe pneumoniae, septic shock and acute respiratory distress syndrome (ARDS) (2). Increased age is the most important risk factor for a complicated disease course (3-6). According to a Chinese epidemiologic study in February 2020, the case fatality rate ranges from 3.6% in patients between 60 and 69 years old, over 8% in the 70-79 years old to 14.8% in patients above 80 years.

The first Belgian SARS-CoV-2-infection was reported on February 2, 2020. Over the next weeks, the virus spread throughout the country. This forced the government to declare a first lockdown on the 17th of March 2020. Nevertheless, Belgium was struck hard and experienced its first peak in infections and hospitalizations over the next three months. At the end of May 2020 almost 60 000 cases were confirmed, of which more than 9 000 deaths *(https://covid19.who.int/)*. During the summer months, infection rates were relatively low in Belgium, but they started to increase in September with a 'second wave' from October until December 2020.

Both in the first and in the second wave, supportive care was the keystone of therapy and consisted of antipyretics (paracetamol), fluid therapy, treatment of bacterial coinfections and oxygen support. Despite a perceived increased risk of aerosolization, ICU protocols of Ziekenhuis Oost-Limburg (ZOL) Genk, Belgium, recommended to use High Flow Nasal Cannula (HFNC) as first step in case of oxygenation failure in COVID-19 patients, both in the first and in the second wave. Intubation was only performed if oxygenation or ventilation was insufficient despite maximal use of HFNC. Ceftriaxone was the antibiotic of choice in the first wave, cefuroxime in the second wave. Moxifloxacine was used in case of cephalosporin-allergy. They were started in every patient to prevent bacterial coinfection.

The limited scientific knowledge during the first wave came from the first experiences in China some months earlier. Experimental treatment consisted of hydroxychloroquine, ritonavir/lopinavir and remdesivir. Although a curative therapy for COVID-19 was still lacking, it became clear during the following months that many of these experimental antiviral treatments had no or even a negative effect (7-10).

As corticosteroids are associated with a prolonged viral RNA shedding, they were only prescribed after five days in some COVID-19 patients in whom pulmonary inflammation and fibrosis was thought to play an important role during the first wave (11). SARS-CoV-2 elicits an aberrant immune response with an overproduction of proinflammatory cytokines in severe COVID-19 disease (12-15). Therefore, the focus of treatment shifted to anti-inflammatory drugs. The RECOVERY Collaborative group demonstrated that in-hospital patients receiving oxygen therapy (with or without mechanical ventilation) have improved survival with dexamethasone. Twenty-eight days mortality decreased from 25.7% in the usual care group to 22.9% in the dexamethasone group. In the patients receiving mechanical ventilation, the incidence of death even decreased from 41.4% to 29.3% (16). In the second wave, dexamethasone had become part of the standard treatment in hospitalized patients for up to 10 days in this center.

The excessive inflammation, platelet activation, endothelial dysfunction and stasis in COVID-19 patients predisposes these patients to venous and arterial thrombo-embolism. In ICU, the incidence of deep venous thrombosis and pulmonary embolism is in the range of 25% to 60%, despite anticoagulant prophylaxis (17-20). In the first wave, every patient received a standard prophylactic dose of anticoagulation (0.5 mg/kg once daily). In the second wave, this dose was doubled (0.5 mg/kg twice daily), combined with daily anti-Xa measurements and an ultrasound screening for deep venous thrombosis twice a week.

The aim of this retrospective analysis was to determine whether this improved scientific knowledge and adjusted therapy was associated with an improved survival of elderly patients in the ICU. We retrospectively compared survival of aged COVID-19 patients (> 70 years old) in the ICU of a tertiary non-academic Belgian hospital during the first wave (March, April and May 2020) with those of the second wave (October, November, December 2020).

Methodology

Study design and participants

This retrospective study included two cohorts of elderly COVID-19 patients, aged 70 years and older, admitted to the ICU of ZOL Genk. The first cohort of patients was admitted between March 1, 2020 and May 31, 2020 (first wave). The second cohort was admitted between October 1, 2020 and December 31, 2020 (second wave). Every admission to ICU was assessed on individual base and discussed with patient or family members, intensivist and pulmonologist/geriatrician. All

patients needed at least intensive oxygen support by high-flow nasal cannula. Asymptomatic carriers of SARS-CoV-2 and those admitted to ICU for non-respiratory vital support were excluded (e.g. cardiogenic shock with COVID-19 without need for intensive oxygen support).

Overall mortality risk was assessed using disease severity scores (Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) IV) as well as comorbidity scores (Charlson Comorbidity Index (CCI) and the Rockwood Clinical Frailty Scale).

The COVIP study (reference number 20/0025L, and ctu2020036) was approved on 17-04-2020, by the ZOL Genk independent ethics committee and adhered to the STROBE guidelines on retrospective analyses. Informed consent was waived by the Ethics Commission.

Data collection

Comprehensive data was collected at baseline, including demographics, chronic health conditions, vital signs, ventilatory and laboratory investigations. They were retrospectively extracted from the electronic medical records (Hix Chipsoft) in a standardized manner where possible, checked and when necessary completed manually by three researchers (VG, WX and VH). Outcome data was completed manually by these researchers, based on medical records or telephone consultation after discharge.

Definitions

All patients were diagnosed with COVID-19 by being symptomatic (fever, chough, dyspnea, expectorations, respiratory distress or myalgia) and having a positive result on SARS-CoV-2 polymerase chain reaction (PCR) test. Wave one was the cohort of patients admitted to the ICU between March 1, 2020 and May 31, 2020. Wave two consisted of patients admitted to the ICU from October 1, 2020 until December 31, 2020.

Primary outcome was survival at 90 days post-admission. In hospital mortality was automatically registered in the medical records. Out of hospital mortality was assessed by telephone consultation three months after admission. Secondary outcome was 30 day survival, survival of ICU stay and length of stay in the ICU.

Chronic lung disease was defined as having bronchial asthma or chronic obstructive lung disease (COPD), with or without inhalation therapy or interstitial lung disease.

Chronic renal disease was defined as chronic kidney failure grade 3a to grade 5 or chronic dialysis.

SOFA, APACHE IV and CCI were calculated using automatically extracted laboratory results and vital functions from the electronic medical records. Medical history was completed manually after which the score was validated by a physician or dedicated researcher. APACHE II proved to be a better predictor of in-hospital mortality of COVID-19 patients then SOFA (21). Since APACHE IV is the latest version of APACHE scores, APACHE IV was likewise considered a good predictor of mortality and disease severity.

The Rockwood Clinical Frailty Scale was assessed on admission by an ICU-physician or retrospectively scored by a researcher based on the medical records and patient history.

Invasive ventilation was defined as intubation with mechanical ventilation for at least 24 hours. HFNC therapy was not considered as invasive ventilation.

Do Not Resuscitate (DNR) codes were registered and dated in the medical records. As extracorporeal membrane oxygenation (ECMO) was a therapeutic option, available in this center, many elderly patients received a DNR 2 code for ECMO. This still allowed invasive ventilation or dialysis to be initiated in these patients.

Statistical analysis

Statistical analysis was performed using JMP, version 15.0.0 (SAS Institute Inc, Cary, NC, USA). Continuous numerical variables with a normal distribution were represented as mean with a standard deviation (SD). They were analyzed by Student t-test. Non-parametric continuous data were represented as median with an interquartile range (IQR) and analyzed by Wilcoxon signed rank / Kruskal-Wallis tests. Qualitative binomial variables (arterial hypertension, renal disease, chronic obstructive lung disease, diabetes, gender and invasive ventilation) were represented as absolute number and frequency using two-tailed Fischer's Exact test. Two-sided p-values less than 0.05 were defined as significant.

Results

Characteristics on admission

In total, 90 COVID-19 patients aged 70 years and older were admitted to the ICU of ZOL Genk. All of them were included in this study. Forty-four

Table 1

Difference in baseline characteristics between wave 1 and wave 2

	Wave 1 (n=44)	Wave 2 (n=46)	P-value
Age, y	77 (SD 4.7)	77 (SD 5.1)	0.90
Gender • Male • Female	 30 (68.18%) 14 (31.82%)	 29 (63.04%) 17 (36.96%)	0.66
BMI *	28.9 (SD 5.3 Kg m^2-1)	28.6 (SD 4.7 Kg m^2-1)	0.83
Height, m	1.67 (SD 0.10)	1.66 (SD 0.99)	0.70
Weight, kg	80 (SD 12.3)	79 (SD 15.2)	0.69
Chronic lung disease	10 (22.73%)	11 (23.91%)	1.00
Chronic renal disease	23 (52.27%)	14 (30.43%)	0.0533
Diabetes	15 (34.09%)	13 (28.26%)	0.65
Arterial hypertension	24 (54.55%)	34 (73.91%)	0.0779
Invasive ventilation	15 (34.09%)	11 (23.91%)	0.35
External transfer	1 (2.27%)	10 (21.7%)	0.0076
Apache IV score **	35 (IQR 16)	34 (IQR 18)	0.53
SOFA score ***	3.5 (IQR 2)	3 (IQR 3)	0.14
CCI ****	5 (IQR 3)	5 (IQR 3)	0.64
Rockwood Clinical Frailty Scale	3 (IQR 2)	3 (IQR 1)	0.09

** BMI: Body mass index; ** APACHE IV: Acute physiology and chronic health evaluation IV; *** SOFA: Sequential Organ Failure Assessment; **** CCI: Charlson Comorbidity index.*

Table 2

Comparison of survival, length of ICU stay and DNR coding at admission between wave 1 and 2

	Wave 1 (n=44)	Wave 2 (n=46)	P-value
Vital status at 90 days	23 (52.27%)	24 (52.17%)	0.99
Vital status at 30 days	25 (56.82%)	26 (56.52%)	1.00
Survived to discharge	28 (63.64%)	27 (58.70%)	0.67
Length of ICU stay (h)	190 (IQR 443)	174 (IQR 210)	0.79
DNR code 0 at admission	30 (68.18%)	25 (54.35%)	
DNR code 1 at admission	3 (6.82%)	3 (6.52%)	
DNR code 2 at admission	11 (25%)	18 (39.13%)	

patients and forty-six patients were admitted in the first and second wave respectively. A comparison of baseline patient characteristics was made in table 1. Mean age of the elderly COVID-19 ICU-patient was 77 years and two thirds of them were male, both in wave one and wave two. There was no significant difference in gender, height, weight and body mass index between the two waves. Patients' pre-existing comorbidities were also comparable between the two waves. Chronic renal disease trended to be more prevalent in the first wave, whereas arterial hypertension was more frequent in the second wave. However, both findings were not significant. Obesity and overweight are known risk factors for a more severe disease course of COVID-19, which is demonstrated in the baseline characteristics. Mean body mass index was 28.9 Kg m^2-1 and 28.6 Kg m^2-1 in respectively wave one and wave two. Disease severity scores (SOFA and APACHE IV) and comorbidity scores (CCI and Rockwood Clinical Frailty Scale) were similar between the two waves. In the second wave however, significantly

more patients (21.7%) were transferred from external hospitals compared to the first wave (2.3%) (p = 0.0076).

Comparison of outcome

Table 2 shows a comparison in vital status at 90 days (primary outcome), as well as a comparison of 30 day survival, ICU length of stay, survival to ICU discharge and DNR codes at admission (secondary outcomes).

No significant difference in 90 day survival was found between the first and the second wave. In the first wave, 90 day survival was 52.27%, in the second wave it was 52.17% (p = 0.99). Thirty day survival was also almost identical between two waves, namely 56.82% in wave 1 and 56.52% in wave 2 (p = 1.00). In the first and the second wave respectively 63.64% and 58.70% of patients survived their ICU stay. This small difference was not significant (p = 0.67). Median duration on ICU was 7.92 days (190 h) and 7.25 days (174 h) respectively (p = 0.79). In the second wave, more patients received a DNR code 2 at the time of admission, 39.13% compared to 25% in the first wave.

Discussion

In this study, we compared survival rates of elderly (> 70 years old) COVID-19 patients, admitted to the ICU in the first wave (March, April and May 2020) with those of the second wave (October, November and December 2021). We wondered whether the improved medical knowledge of COVID-19 and the adjusted medical therapy resulted in a better outcome for these patients in the second wave. The most important adjustments were the standard use of dexamethasone, the increased vigilance for deep venous thrombosis and increased dose of prophylactic anticoagulation therapy. Hydroxychloroquine, lopinavir-ritonavir and remdesivir were no longer used in the second wave. However, there was no significant difference in outcome between the two waves. Ninety-day survival was 52.27%, and 52.17% in respectively the first and second wave. Hereafter, these findings are compared with national and international data.

A report of Sciensano (the Belgian institute for epidemiology and public health) based on the collected Belgian hospital data from the beginning of the COVID-19 pandemic until March 2021, reported a mean ICU survival of 62.3% in the group between 50 and 79 years old and 33.3% in those above 80 years old (22). In ZOL, approximately one third of patients were 80 years or older and survival to ICU discharge was 63.64% and 58.70% in respectively the first and the second wave. Although baseline characteristics of national data were not entirely available for comparison, ICU survival in ZOL seems to be in line with national data. Sciensano reported a trend towards a higher ICU-case fatality rate in the second wave, but they recognized that the rates of the second wave could have been overestimated due to reporting bias. Length of stay was comparable with our findings, median length of stay was 10 days in the group of 50 to 79 years old, and 7 days in the group of 80 years old. The decreased length of stay in the latter is probably due to an increased mortality in ICU in this group.

Availability and organization of ICU beds and admission policies differ significantly between countries. For example, the Netherlands have a more restrictive policy for elderly on ICU then Belgium. In addition, a scarcity of resources at peak pandemic times can have a negative effect on survival rates. All these factors may bias survival rates and makes it difficult to compare between countries. This study was a sub-analysis of the European COVIP-trial, a multicenter study with 1346 patients from 138 ICU's across 28 countries, recruited during the first wave (from March 19, 2020 until May 26, 2020). Here, the overall 90- and 30-day survival was 52% and 59% respectively, which is comparable with our findings (23). An Italian retrospective study on ICU mortality in Lombardy during the first months of 2020 reported a thirty-day survival of 38.6% for patients above 64 years old (6). Lombardy was one of the first European regions with an outbreak of COVID-19, which seriously stretched the healthcare system. Apart from the higher mortality rates, the authors also reported a higher proportion of patients on mechanical ventilation (87.3% among all ages). It is impossible to conclude whether these differences are due to the intubation policy. Moreover, patients admitted to medium care with non-invasive ventilation options were not included in this study. An updated systematic review and meta-analysis of Armstrong et al. including 52 observational studies and 43128 patients reported a mean ICU-survival rate of 64.5% (61.1%-68.7%) among all ages (24, 25). Multivariate meta-regression failed to show a significant effect of age, but other studies have clearly demonstrated the effect of age on survival (3-6). Keeping this in mind, ICU survival rates for the elderly in ZOL seem to be in line with international averages. The systematic review of Armstrong

Table 3

ICU protocol for COVID-19 patients in wave 1 and wave 2

Wave 1	**Wave 2**
Fluid therapy**:** Plasmalyte-glucose 5%	Fluid therapy: Plasmalyte-glucose 5%
Antipyretics (paracetamol)	Antipyretics (paracetamol)
Ulcer prophylaxis • Pantoprazole 40 mg IV or • Omeprazole 40 mg PO	Ulcer prophylaxis • Pantoprazole 40 mg IV or • Omeprazole 40 mg PO
Oxygenation support: • HFNC* (first line) • Mechanical ventilation (second line) ○ Volume-controlled ventilation ○ Tidal volume 6-8 ml/kg ○ Titrated PEEP** • ECMO*** (third line, in selected cases)	Oxygenation support: • HFNC (first line) • Mechanical ventilation (second line) ○Pressure-controlled ventilation ○Tidal volume 6-8 ml/kg ○Titrated PEEP • ECMO (third line, in selected cases)
Antiviral, anti-inflammatory drugs: • Hydroxychloroquine • Lopinavir/ritonavir • Remdesivir in selected cases • Corticosteroids after day 5 of ICU-stay in patients with high pulmonary inflammation and fibrosis	Antiviral, anti-inflammatory drugs: • Dexamethasone
Antibiotic therapy • Ceftriaxone 2000 mg (1x/day)	Antibiotic therapy • Cefuroxime 1500 mg (3x/day)
Venous thrombosis prophylaxis • Enoxaparine 0.5 mg/kg (1x/day)	Venous thrombosis prophylaxis • Enoxaparine 0.5 mg/kg (2x/day) • Daily anti-Xa measurement • Systematic screening for DVT twice a week

* HFNC: High flow nasal cannula; ** PEEP: Positive end-expiratory pressure; *** ECMO: extra-corporal membrane oxygenation.

shows however an increase in survival over time in 2020 with 0.30% per month. This improvement in survival was absent in our study population and in the Belgian ICU population.

Patient comorbidities are comparable and disease severity scores were similar between both waves. Also, there is no evidence of an increased nor decreased virulence of SARS-CoV-2. Both waves in Belgium were mainly caused by the D614G variant of the initial SARS-CoV-2-strain originating from Wuhan, China (26, 27). Although the British, South-African or Brazilian variant will probably supersede the D614G variant, they were not dominant in the Belgian population during the first two waves. Apart from dexamethasone, no drug has been demonstrated to have a clear benefit in critically ill COVID-19 patients so far (16). The RECOVERY group demonstrated an absolute reduction in mortality of more than 12.1% in COVID-19 patients receiving mechanical ventilation, but the absolute reduction was just 2.8% in the hospitalized patients. In our study population, only 15 (34.09%) and 11 patients (23.91%) were mechanically ventilated in respectively the first and second wave. In addition, a significant proportion of intensive care COVID-19 patients received corticosteroids in the first wave, since corticosteroids might be beneficial in (a subgroup of) ARDS-patients (28). The use of corticosteroids in the first wave and the small group of mechanically ventilated patients may explain the lack of reduction in mortality during the second wave. The question remains whether all critical ICU-patients profit from the corticosteroid treatment, since its use can delay viral clearance, increase the risk of opportunistic infections, suppress the hypothalamic-pituitary-adrenal axis and increase hyperglycemic episodes (11, 29-31).

In the second wave, significantly more patients were transferred from external hospitals, due to the increased establishment of the Hospital & Transport Surge Capacity Plan, a nationally organized plan to redistribute COVID-19 patients. These patients had however similar survival rates as the non-transferred patients. Do-not reanimate codes are important to avoid medical futility and to properly allocate available resources, especially in times of scarcity. This coding was improved in the second wave. Caution should be used when interpreting these data

as this hospital serves as an ECMO center and DNR 2 coding was often given for ECMO solely. In ZOL, no elderly patient received ECMO treatment.

This was a retrospective single center analysis, with a total of 90 elderly patients. The sample size is underpowered to detect smaller benefits of the adjusted therapy during the second wave. In this analysis, general treatment protocols were used to determine the major therapeutic differences between the first and second wave. Although field experiences indicated that these protocols were well followed, it was not possible to determine whether patients actually received the proposed treatment. The retrospective approach makes this analysis vulnerable to information bias as missing data is possible. The lack of improvement during the second wave in this analysis does not preclude a changed survival rate in the younger COVID-19 ICU group, as only elderly patients were studied.

We conclude that despite improved disease insights, dexamethasone being part of the standard therapy and the increased awareness for deep venous thrombosis and pulmonary embolism survival rates did not change over time in the elderly COVID-19 ICU-patients in ZOL Genk. The ICU survival rates of these patients were comparable with national and international rates.

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