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SPECIAL REPORT

One year of COVID-19 in the Netherlands - a Dutch narrative

On behalf of the Dutch COVID-19 Research Consortium
Dutch National Intensive Care Evaluation, Department of Clinical Informatics, Amsterdam University Medical Center, University of Amsterdam, the Netherlands

See appendix for a list of the members of the Dutch COVID-19 Research Consortium

Correspondence
secretariaat@stichting-nice.nl

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'It is easy to be wise after the event'
(Sir Arthur Conan Doyle)

A novel zoonotic corona virus hits the Netherlands

In December 2019, China reported a cluster of cases of pneumonia in the city of Wuhan (Hubei Provence). In the beginning the biological agent was not known, but in January 2020 a corona virus was identified as the pathogen causing this pneumonia. Because of its resemblance to a previous corona virus epidemic, this new virus was called 'severe acute respiratory coronavirus 2 (SARS-CoV-2) and the disease was called 'corona virus disease 2019' (COVID-19). By that time, however, SARS-CoV-2 was no longer contained to China and the first confirmed patients with COVID-19 were seen outside China in Thailand, Japan and South Korea. Despite the fact that the Chinese authorities locked down the entire city of Wuhan, the worldwide spread of COVID-19 was rapid and unstoppable.

On 14 February 2020, the French reported the first European death to COVID-19. An 80-year-old Chinese tourist died in a hospital in Paris. Two days later a major surge of patients was noticed in Italy. After more than 150 patients fell ill with COVID-19 in the Lombardy area, the Italians locked down ten North-Italian towns. A 56-year-old man, who had returned from Italy, was the first Dutch patient to be confirmed of having COVID-19 on 27 February 2020. In the days thereafter several patients were diagnosed with COVID-19 and all had recently visited Italy. One week later the first Dutch patient with confirmed COVID-19 died as a consequence of the disease. By that time, over 320 patients were diagnosed with COVID-19 and the Netherlands went into 'intelligent' lockdown. This, however, could not prevent the surge of infected patients. By the end of March over 10,000 Dutch patients were confirmed of having COVID-19 but since testing was mostly only done for the very sick and healthcare workers, the actual number of infections was likely much higher.[1]

The surge of critically ill patients in the Netherlands

Most people (about 80%) recover from the disease without needing special treatment and for the majority – especially children and young adults – illness due to COVID-19 is generally mild. However, for some people it can cause serious illness. Around 1 in every 10 people who are infected with COVID-19 develop difficulty in breathing and require hospital care. Particularly patients who are aged over 60 years, and people who have underlying medical conditions such as diabetes, heart disease, respiratory disease or hypertension, are among those who are at greater risk.[2] Of the patients needing hospital treatment roughly one fifth eventually needed ICU care.[3] In the Netherlands, 0.35% of the infected people needed ICU admission.[4] This resulted in a huge demand for ICU beds that were not available in the Netherlands in April 2020 *(figure 1)*.

In the pre-COVID era the Netherlands had roughly 1050-1100 ICU beds available, although some were not 'fully operational' due to shortages of ICU personnel. Usually 80% of these ICU beds are occupied by critically ill patients with non-COVID reasons for ICU admission, resulting in only 400 available beds to allocate to COVID-19 patients (*figure 2*). This huge shortage of ICU beds and personnel necessitated the Dutch hospitals to suspend all non-essential treatments and redirect all the workforce to the COVID-19 wards and ICUs. Additional ICU beds were created at new locations, such as post-anaesthesia care units, recovery units, operating theatres and newly created ICUs. The first wave of critically ill COVID-19 patients was managed with the help of many non-ICU trained personnel and necessitated stricter selection of patients than prior to the pandemic.

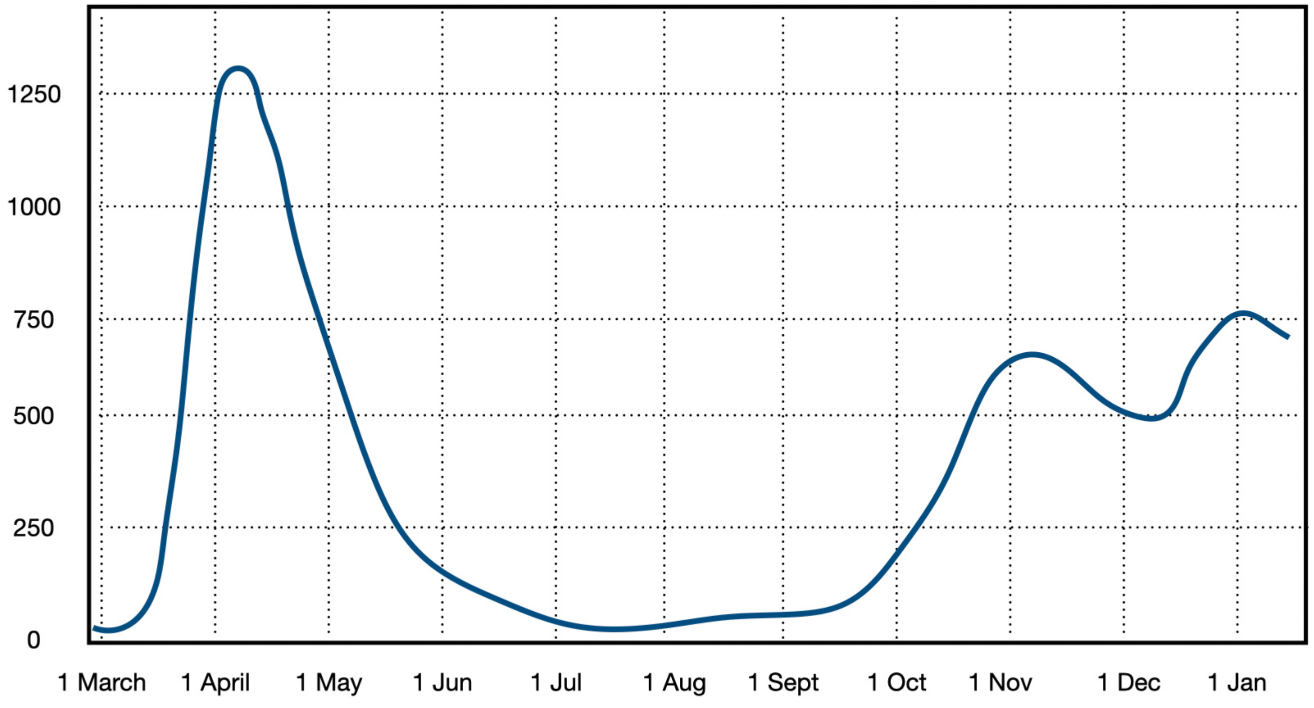


Figure 1. Patients with proven COVID admitted to the Dutch ICUs

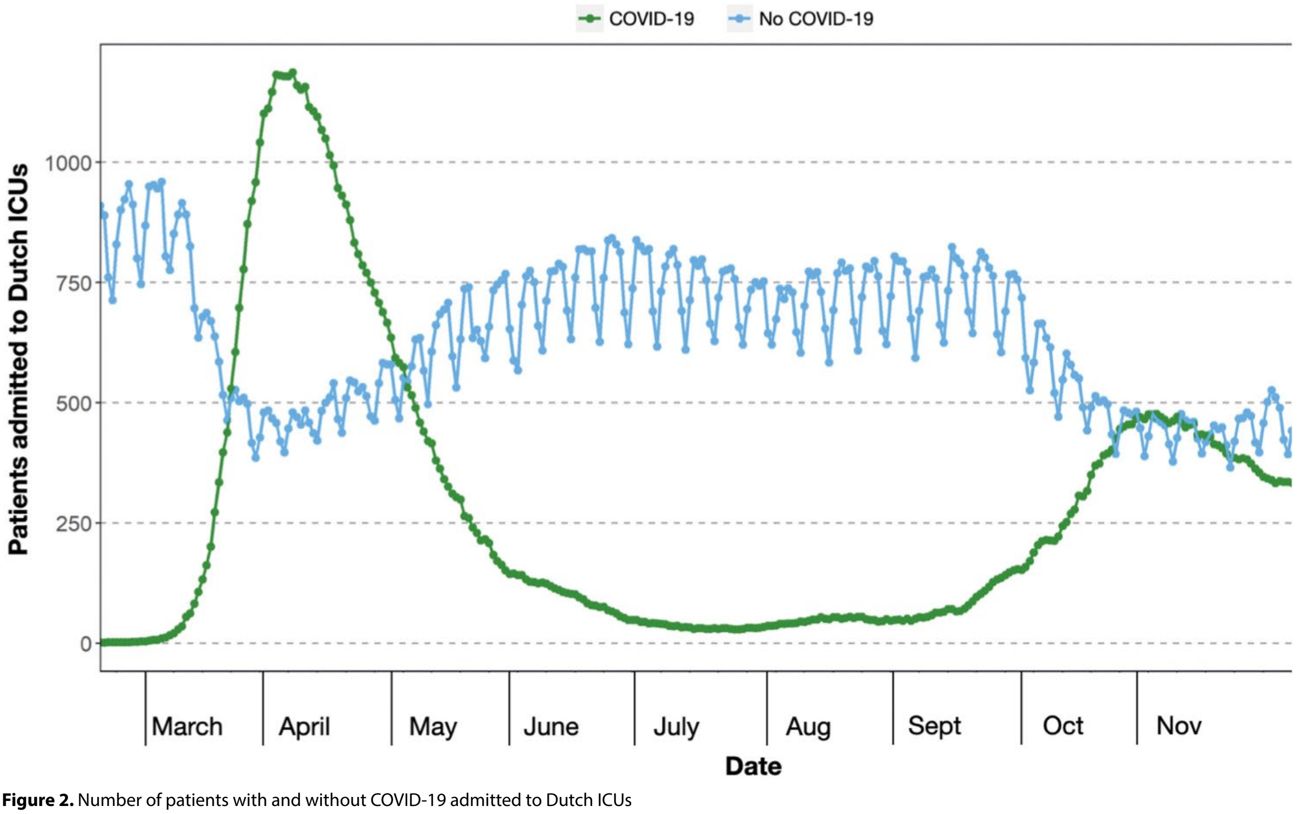


Figure 2. Number of patients with and without COVID-19 admitted to Dutch ICUs

Despite the fact that non-essential medical care was downscaled, the majority of ICUs continued with regular care that could not be postponed. *Figure 2* shows that the average 800 occupied ICU beds decreased to roughly 500 non-COVID beds during the height of the first wave.

Demographics of Dutch COVID-19 patients

In the beginning of the pandemic, the impression was that especially obese, older men were overrepresented in the critically ill patients. Now, 12 months into the COVID-19 pandemic this has shown to be rather consistent over time. The mean age of

Table 1. Comparison between COVID-19 patients and historical admission with severe acute respiratory infection (SARI), e.g. influenza pneumonia, community-acquired pneumonia, etc.

	COVID-19 patients N (%)	SARI patients N (%)
COPD/respiratory insufficient	661 (12.4)	7549 (38.1)
Renal failure	236 (4.4)	1717 (8.7)
Cirrhosis	19 (0.4)	239 (1.2)
Cardiovascular insufficiency	77 (1.4)	760 (3.8)
Malignancy/haematological malignancy	142 (2.7)	1960 (9.9)
Immunological insufficiency	459 (8.6)	3807 (19.2)
Diabetes	1211 (22.7)	4006 (20.2)
Mechanical ventilation at ICU admission	2106 (39.5)	7941 (40)
Mechanical ventilation within the first 24 h of ICU admission	3648 (68.5)	11153 (56.2)
Total	7380 (100)	19835 (100)

COVID patients is 63.8 (SD 11.5) years, which is only minimally older than the mean age of non-COVID, critically ill patients (60.3 years, SD 17.2 years). In comparison with historical patients with severe acute respiratory illnesses (so-called SARI, such as pneumonia, influenza, etc.), the COVID-19 patients appear slightly younger (mean age of SARI patients was 66.3 years), and they have less comorbidities (*table 1*).

The number of comorbidities in COVID-19 patients increases with increasing age and is depicted in *figure 3*. When the first wave subsided and ICU crowding was less imminent the, often subconscious, admission selection of patients became less strict. This is reflected in the fact that more albeit younger patients with comorbidities were admitted between the first and the second wave (data not shown).

Outcome of COVID-19 patients

The mortality of critically ill COVID-19 patients differs enormously between publications. This is the result of different inclusion criteria, differences in healthcare settings, ICU crowding and in outcome definitions.[5-7] Especially healthcare systems and ICUs that were stretched to the maximum of their capacity (and beyond) potentially delivered suboptimal care, which could have resulted in higher mortality rates.[8] For example, in the Italian area of Lombardy the ICU mortality was 48.7% and hospital mortality was estimated to be 53.4%.[6] It has been suggested that a large part of these deaths could have been prevented if ICUs had been less congested and accessibility to hospitals and ICUs had been more immediate.[9] The same might be true in the Netherlands. We, at least, see that some areas in the Netherlands had higher crude mortality rates than other regions (*figure 4*).

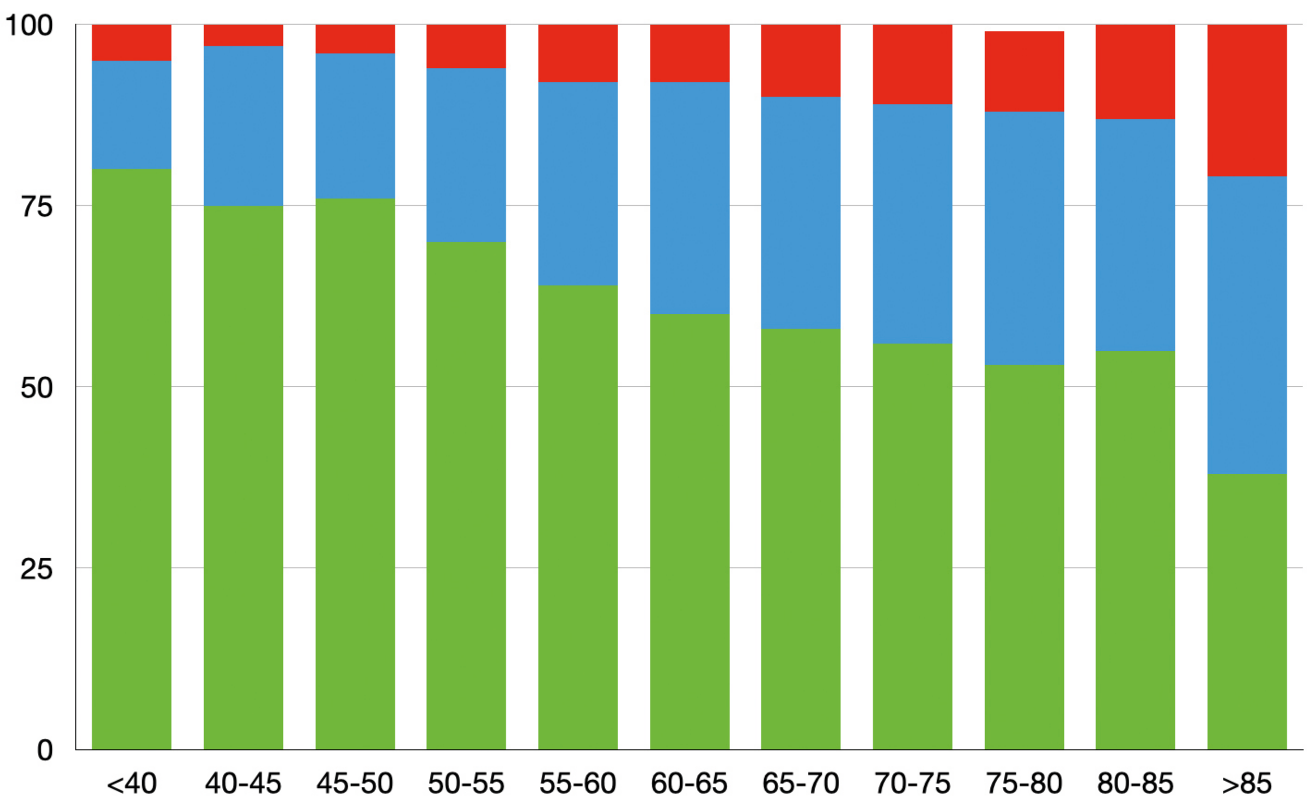


Figure 3. The number of comorbidities increases with age: no comorbidities (green), one comorbidity (blue) or two or more comorbidities (red)

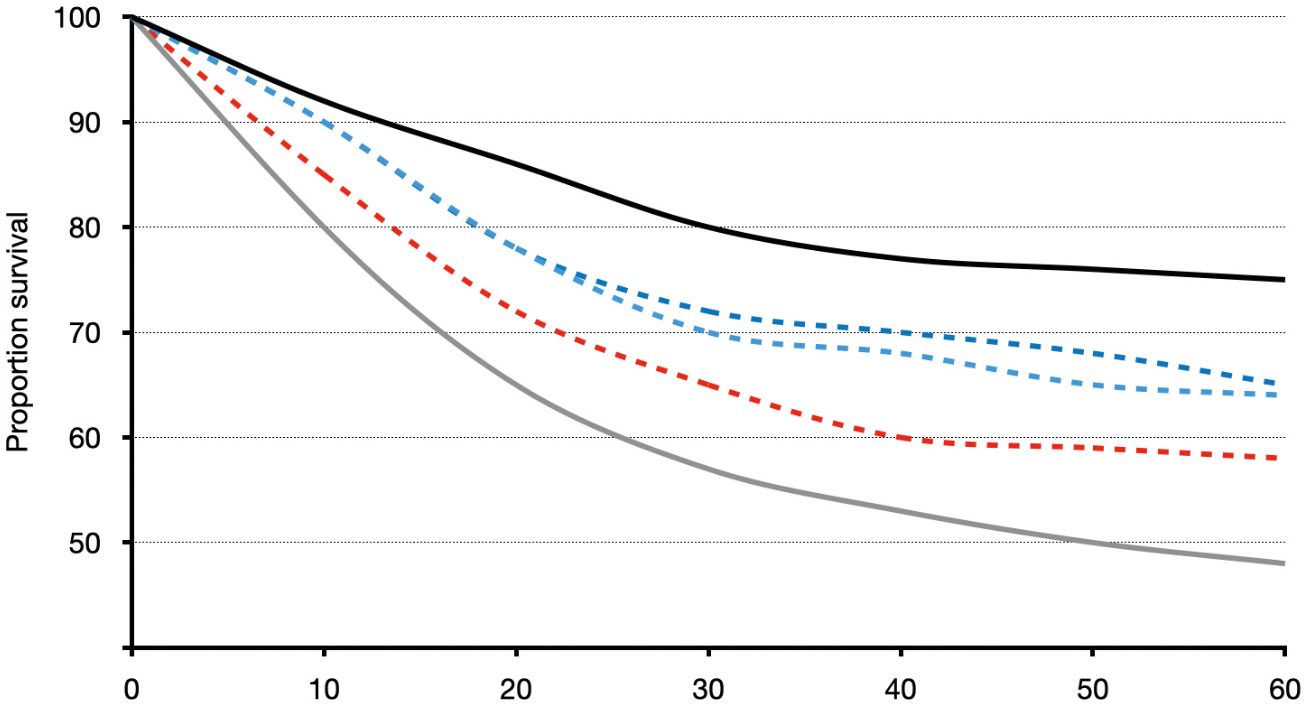


Figure 4. Kaplan-Meier survival curves of crude survival after ICU admission. Only 5 out of the 12 Dutch ICU regions are depicted here to illustrate the huge ranges in crude 60-day survival.

Apart from access to immediate ICU care, several other variables were associated with better or worse outcome of critically ill COVID-19 patients. Obviously, older patients have a higher risk of mortality than younger patients and the odds for death increase significantly for patients aged 60 years and above (*table 2*). Particularly the patients 70 years and older have a 10 to 25 times increased risk of hospital mortality.

Another striking feature is that women have a better outcome than men (odds ratio 0.68, confidence interval 0.58-0.8). This has been noted in various other publications and meta-analysis.[10,11] In a univariate analysis obesity was also associated with ICU admission.[12] However, despite the initial thought that obesity was associated with a worse outcome, the survival of overweight patients appeared to be better (e.g. patients with a BMI 30-35 had an odds ratio of 0.68 in comparison with patients with a BMI 18.5-25). This might also be explained by the younger age of those patients but it does contradict previous findings in COVID-19 patients.[12] However, previous research in general Dutch ICU patients showed a U-shaped survival curve in relation to BMI.[13] Whether this is a reflection of the normal outcome of ICU patients or the result of confounding needs to be elucidated. The diminished mortality in (slightly) overweight COVID-19 patients might have resulted from admission bias (only accepting the younger, healthiest obese patient onto the ICU). Again, like in every other disease, patients with comorbidities have a higher mortality than patients without such mortalities.

International publications suggest that some groups of patients (patients from non-Dutch descendants) might have a worse course of COVID-19 and are overrepresented within the critically ill subpopulation.[14] In the Netherlands, it is prohibited to collect these data due to privacy restraints. Whether this represents confounding or has a pathophysiological origin remains to be elucidated.

Survival trends over time

After the first wave, when the capacity of ICUs was stretched to the limit, the numbers of critically ill COVID-19 patients declined. This meant that ICUs that had diluted their personnel (sometimes to a nurse-to-patient ratio of >1:4) could return to normal care. This was paralleled by better treatment modalities of COVID-19 patients. During the first wave various randomised controlled trials proved that some hypothetical treatments were ineffective (e.g. chloroquine, lopinavir/ritonavir) while others were effective in critically ill patients (e.g. dexamethasone and potentially the prevention of thromboembolism by increased anticoagulation strategies).[15,16] Combined, these results have led to better outcomes over time in COVID-19 patients on hospital wards. The case-mix of COVID-19 patients that ends up on the ICU in the second wave is different than that in the first wave. This results in variations in the Kaplan-Meier curves over time (*figure 5*).

Table 2. The odds for hospital mortality for various risk factors

NAS item	COVID-19 survivors N (%)	COVID-19 deceased N (%)	Odds ratio (95% CI)	COVID-19 still in hospital N
Age groups				
<40	178 (92.7)	14 (7.3)	Reference	9
40-45	101 (91)	10 (9)	Reference	2
45-50	238 (89.5)	28 (10.5)	Reference	11
50-55	383 (87.8)	53 (12.2)	1.38 (0.92-2.06)	19
55-60	520 (84)	99 (16)	1.9 (1.33-2.7)	35
60-65	596 (75.3)	195 (24.7)	3.26 (2.35-4.51)	50
65-70	549 (65.7)	287 (34.3)	5.21 (3.8-7.15)	48
70-75	557 (56.8)	423 (43.2)	7.57 (5.55-10.31)	54
75-80	290 (46.9)	328 (53.1)	11.27 (8.15-15.57)	27
80-85	65 (36.3)	114 (63.7)	17.47 (11.53-26.47)	7
>85	6 (26.1)	17 (73.9)	28.23 (10.67-74.65)	0
Gender				
Men	2419 (67.2)	1181 (32.8)	Reference	204
Woman	1075 (73.5)	338 (26.5)	0.74 (0.65-0.85)	59
BMI groups				
<18.5	14 (53.8)	12 (46.2)	1.58 (0.72-3.44)	2
18.5-25	694 (65.2)	371 (34.8)	Reference	61
25-30	1446 (68.6)	663 (31.4)	0.84 (0.73-0.98)	95
30-35	824 (73.5)	297 (26.5)	0.66 (0.56-0.79)	58
35-40	293 (69.8)	127 (30.2)	0.8 (0.63-1.01)	29
>40	135 (75)	45 (25)	0.61 (0.43-0.88)	11
Comorbidities				
COPD & respiratory insufficiency (no)	3123 (70.3)	1317 (29.7)	Reference	225
COPD & respiratory insufficiency (yes)	371 (59.6)	252 (40.4)	1.61 (1.36-1.91)	38
Renal failure (no)	3405 (670.3)	1441 (29.7)	Reference	244
Renal failure (yes)	89 (41)	128 (59)	3.4 (258-4.48)	19
Cardiovascular insufficiency (no)	3464 (69.4)	1528 (30.6)		29
Cardiovascular insufficiency (yes)	30 (42.3)	41 (57.7)	3.1 (1.93-4.98)	6
Malignancy (no)	3433 (69.7)	1495 (30.3)	Reference	256
Malignancy (yes)	61 (45.2)	74 (54.8)	2.79 (1.97-3.93)	7
Immunological insufficiency (no)	3247 (70.1)	1385 (29.9)	Reference	235
Immunological insufficiency (yes)	247 (57.3)	184 (42.7)	1.75 (1.43-2.14)	28
Diabetes (no)	2783 (71.3)	1122 (28.7)	Reference	210
Diabetes (yes)	711 (61.4)	447 (38.6)	1.56 (1.36-1.79)	53
Comorbidities				
None	2261 (75.1)	750 (24.9)	Reference	149
1	990 (63.8)	562 (36.2)	1.7 (1.49-1.94)	80
>1	243 (48.6)	257 (51.4)	3.18 (2.61-3.86)	34

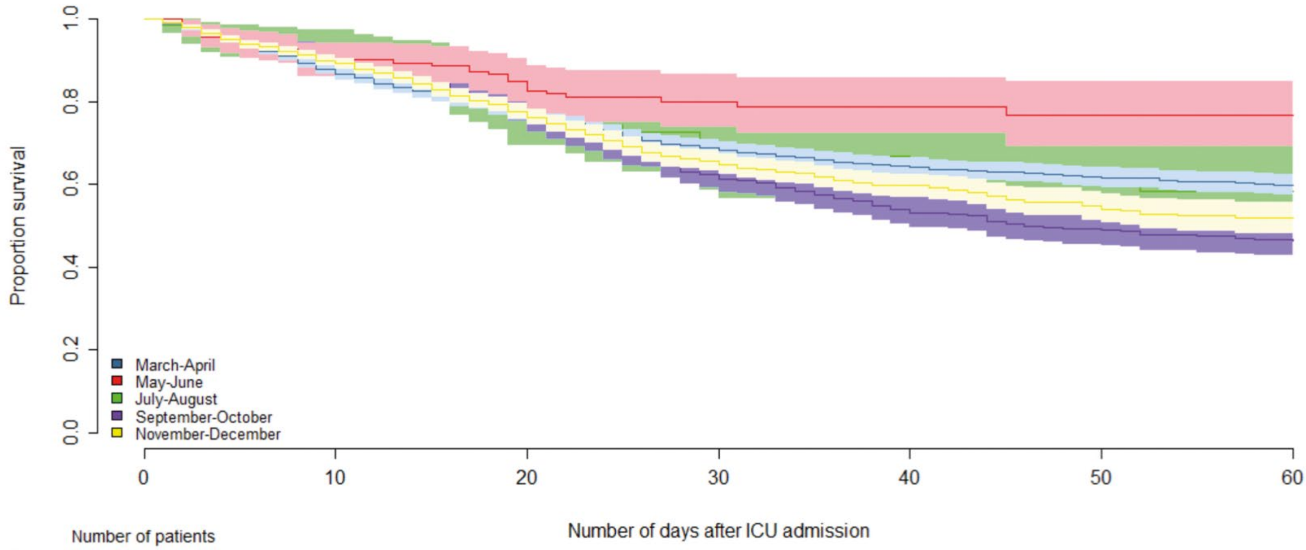
If the 95% confidence interval (95% CI) does not contain 1.0 then the risk factor is statistically significantly associated with hospital mortality in comparison to the reference group. The definitions of the risk factors are derived from the APACHE IV model for severity of illness and can be found in the data dictionary available at www.stichting-nice.nl

Outcome beyond survival

We know that patients who survived COVID-19 have serious sequelae. Many people have not been able to perform their daily activities or resume their work at all or at least for a long time. More than half of the survivors report decreased functional capacity and many describe persistent functional limitations.[17-19] We know that a substantial number of the general ICU survivors suffer from cognitive, psychological and physical impairments, which combined are called the 'post-intensive care syndrome', although in the general ICU population it appears that some patients were already experiencing these symptoms prior to admission.[20] However, such information and long-term follow-up of surviving COVID-19 patients are not yet available, but studies are under way.[21,22] It is quite conceivable that overcrowding, restrictions in access to early mobilisation and physiotherapy as well as specific treatment modalities for COVID-19 (e.g. prolonged muscle paralysis and mechanical ventilation in prone position for ARDS) contribute to worse outcomes. Results for the Dutch ICU population could be obtained by combining databases of discharged critically ill COVID-19 patients with the databases of insurance companies (vektis.nl). Unfortunately, strict privacy regulations prevent swift analyses which could improve patient care for the next wave.

Continuing SARI surveillance in the future

Since the 2009 pandemic of influenza A/H1N1, the World Health Organisation (WHO) advised to establish Severe Acute Respiratory Illnesses (SARI) surveillance in each country to enable earlier detection of potential epidemics and pandemics.[23] In the Netherlands several initiatives aimed to change their quality registries into near 'real-time' surveillances for such severe infections. While the APACHE IV coding, which is used by the NICE registry, does not allow a very granular registration of pulmonary infections, it can be used to approximate the incidences of severe pulmonary infections.[24,25] The admissions to the ICU for pulmonary infections parallel the incidence curves of influenza-like illnesses throughout the years. However, in order to function as a proper SARI sentinel, the NICE database should be near real-time and needs to be able to combine ICU data with other registries to improve the microbiological diagnoses. Near real-time data processing via Fast Healthcare Interoperability Resource (FHIR) messages between hospitals and the central NICE registry will be implemented in 2021. Combining databases necessitates the use of a unique identifier for patients in all registries. However, the use of a (pseudonymised) social security number (BSN) is not allowed. In the COVID-19 pandemic, however, patients are frequently transferred between hospitals and regions. The Dutch government has allowed the use of the BSN specifically for this pandemic as this was the only option to properly follow up these patients. It is somewhat ironic that we needed another pandemic to improve a surveillance that was intended to detect this pandemic in the first place. A proposal for



Number of patients							
March-April	2675	2197	1512	976	641	401	244
May-June	206	155	109	72	44	28	18
July-August	131	100	47	36	26	20	16
September-Oct.	1427	1161	650	370	250	179	115
November-Dec.	2226	1753	1071	555	295	155	86

Figure 5. Kaplan-Meier survival curves of crude survival after ICU admission in two month periods.

legislative change is under construction in which quality registries such as NICE are better secured in the General Data Protection Regulations and the Dutch Healthcare Quality, Complaints and Disputes Act (in Dutch the WKKG), including the use of a pseudonymised unique identifier.

Conclusions

In times of disasters, such as the current SARS-CoV-2 pandemic, when hospitals are flooded with patients and healthcare systems are in dire need of information, it is invaluable to have an up-and-running registry that swiftly adapts to the current need. In the Netherlands the NICE database was able to rise to the occasion because of the continuous effort of intensivists of all Dutch ICUs. Near real-time information and combining ICU data with other registries will improve early warning and give more insights into quality improvement possibilities in future pandemics.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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Appendix The Dutch COVID-19 Research Consortium collaborators

D.P. Verbiest
L.F. te Velde
E.M. van Driel
T. Rijpstra
P.H.J. Elbers
A.P.I Houwink
L. Georgieva
E. Verweij
R.M. de Jong
F.M. van Iersel
T.J.J. Koning
E. Rengers
N. Kusadasi
M.L. Erkamp
R. van den Berg
C.J.M.G. Jacobs
J.L. Epker
A.A. Rijkeboer
M.T. de Bruin
P. Spronk
A. Draisma
D.J. Versluis
A.E. van den Berg
M. Vrolijk-de Mos
J.A. Lens
R.V. Pruijsten
H. Kieft
J. Rozendaal
F. Nooteboom
D.P. Boer
I.T.A. Janssen
L. van Gulik
M.P. Koetsier
V.M. Silderhuis
R.M. Schnabel
I. Drogt
W. de Ruijter
R.J. Bosman
T. Frenzel
L.C. Urlings-Strop
A. Dijkhuizen
I.Z. Hené
A.R. de Meijer
J.W.M. Holtkamp
N. Postma
A.J.G.H. Bindels
R.M.J. Wesselink
S. Brinkman
E.R. van Slobbe-Bijlsma
P.H.J. van der Voort
B.J.W. Eikemans
D.J. Mehagnoul-Schipper
D. Gommers
J.G. Lutisan
M. Hoeksema
M.G.W. Barnas
B. Festen-Spanjer
M. van Lieshout
N.C. Gritters
M. van Tellingen
G.B. Brunnekreef
J. Vandeputte
T.P.J. Dormans
M.E. Hoogendoorn
M. de Graaff
D. Moolenaar
A.C. Reidinga
J.J. Spijkstra
R. de Waal
D.A. Dongelmans
D.W. de Lange
N.F. de Keizer