Differences and Similarities Among COVID-19 Patients Treated in Seven ICUs in Three Countries Within One Region: An Observational Cohort Study*

OBJECTIVES: To investigate healthcare system–driven variation in general characterstics, interventions, and outcomes in coronavirus disease 2019 (COVID-19) patients admitted to the ICU within one Western European region across three countries.

DESIGN: Multicenter observational cohort study.

SETTING: Seven ICUs in the Euregio Meuse-Rhine, one region across Belgium, The Netherlands, and Germany.

PATIENTS: Consecutive COVID-19 patients supported in the ICU during the first pandemic wave.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Baseline demographic and clinical characteristics, laboratory values, and outcome data were retrieved after ethical approval and data-sharing agreements. Descriptive statistics were performed to investigate country-related practice variation. From March 2, 2020, to August 12, 2020, 551 patients were admitted. Mean age was 65.4 ± 11.2 years, and 29% were female. At admission, Acute Physiology and Chronic Health Evaluation II scores were 15.0 ± 5.5, 16.8 ± 5.5, and 15.8 ± 5.3 ($p = 0.002$), and Sequential Organ Failure Assessment scores were 4.4 ± 2.7, 7.4 ± 2.2, and 7.7 ± 3.2 ($p < 0.001$) in the Belgian, Dutch, and German parts of Euregio, respectively. The ICU mortality rate was 22%, 42%, and 44%, respectively ($p < 0.001$). Large differences were observed in the frequency of organ support, antimicrobial/inflammatory therapy application, and ICU capacity. Mixed-multivariable logistic regression analyses showed that differences in ICU mortality were independent of age, sex, disease severity, comorbidities, support strategies, therapies, and complications.

CONCLUSIONS: COVID-19 patients admitted to ICUs within one region, the Euregio Meuse-Rhine, differed significantly in general characteristics, applied interventions, and outcomes despite presumed genetic and socioeconomic background, admission diagnosis, access to international literature, and data collection are similar. Variances in healthcare systems' organization, particularly ICU capacity and admission criteria, combined with a rapidly spreading pandemic might be important drivers for the observed differences. Heterogeneity between patient groups but also healthcare systems should be presumed to interfere with outcomes in coronavirus disease 2019.

KEY WORDS: coronavirus disease 2019; critical care; delivery of healthcare; healthcare economics and organizations; intensive care units; severe acute respiratory syndrome coronavirus 2

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The coronavirus disease 2019 (COVID-19) pandemic spread over the world in 2020. In many countries, a quick rise in infection rate was identified. Many patients were admitted to hospitals with an important

proportion requiring supportive treatment in an ICU, stretching ICU capacity to its limits, even in many developed countries (1, 2). Scarce ICU resources should be optimally used during a pandemic, ideally in close agreement with regular care, which inevitably affects physicians' decisions. Consequently, it may be conceivable that admission criteria and treatment choices also vary throughout countries.

Previous (multi)national studies have been performed in COVID-19 patients requiring ICU support (3–10), mostly presented per country (**Supplementary Digital Content 1**, http://links.lww.com/CCM/G799). However, these studies often comprised intervention studies in selected patients or cohort studies characterized by heterogeneity concerning population characteristics, such as race/ethnicity, genetic background, and socioeconomic status, reflecting differences in the population at risk. Furthermore, large interhospital variations in patient characteristics and outcomes have been reported, which might indicate different degrees of stress on healthcare systems (11, 12). These differences hamper direct comparison of healthcare systems and their responses to the pandemic.

The Euregio Meuse-Rhine, a region covering parts of Belgium, The Netherlands, and Germany, is characterized by a high population density (3,900,000 inhabitants at 11,000 km²) and intense cross-border passage (13). Over 10% of inhabitants were positively tested for COVID-19 infection during the first pandemic wave (www.sanquin. nl-sanquin/nieuws/2020/11/antistoffen-bij-donors-met-ing-november). When comparing healthcare systems' variation, the Euregio has the advantage that the population at risk is assumed to be somewhat homogeneous as they share a genetic background and have a comparable socioeconomic status (13). Furthermore, heterogeneity due to different ICU admission diagnoses was absent since the majority of patients were admitted for COVID-19 pneumonia. In addition, healthcare professionals' vocational training, access to literature, and international guidelines for ICU practice are similar (14).

ICU bed availability is an important difference between countries in general. For the Euregio, the availability of ICU beds in The Netherlands is 6.4, compared with 15.9 and 29.2 per 100,000 inhabitants for Belgium and Germany, respectively (15). Spatial ICU accessibility also varies across numerous European countries (16). Another potential difference is heterogeneity of COVID-19 disease itself. Although

severe acute respiratory syndrome coronavirus 2 is a virus that causes one disease in name, heterogeneity in the course of COVID-19 infection exists (17), which might be amplified since no specific treatment for COVID-19 exists. Experimental off-label therapies, such as (hydroxy)chloroquine, antiviral drugs, and steroids, were used at the time without substantial evidence (18, 19). Thus, the interaction between varying healthcare systems and uncertainty and heterogeneity within COVID-19 disease and treatment may have led to practice variation.

We, therefore, hypothesize that variable healthcare system responses to a pandemic drive variability in patient characteristics and disease severity, support strategies, therapies, and complications and, independent of these factors, determine outcome within a cohort of COVID-19 patients admitted to seven ICUs within the Euregio, one region across Belgium, The Netherlands, and Germany.

MATERIALS AND METHODS

The Euregio intensive care COVID cohort, part of the Euregio COVID Data Platform (CoDaP) project, was initiated at the beginning of the pandemic in early March 2020. With the opportunity of disease homogeneity of patients admitted to Euregio ICUs within a short period, provided by the COVID-19 pandemic, we aimed to investigate potential cross-border differences, including baseline demographics (20), disease course over time (17), sex (21), outcomes (22), and treatment (23, 24), and unravel potential healthcare systems' and strategies' variances (11, 25, 26) that could contribute to future collaboration and optimization of cross-border patient care. Investigators at the departments of Intensive Care Medicine of seven Euregio hospitals (two Belgian; four Dutch, including one academic hospital; and one German academic hospital), situated within a 50 km radius (**Fig. 1**), shared their plans selecting variables for data-sharing and collaboration on COVID-19. ICU resources and care were dictated mainly by individual countries. However, pandemic stress drove some international transportation of patients within the Euregio Meuse-Rhine (**Fig. 2A**), suggesting that cross-border collaboration, for example, delivering care under a joint healthcare mandate (e.g., European Union), would be helpful.
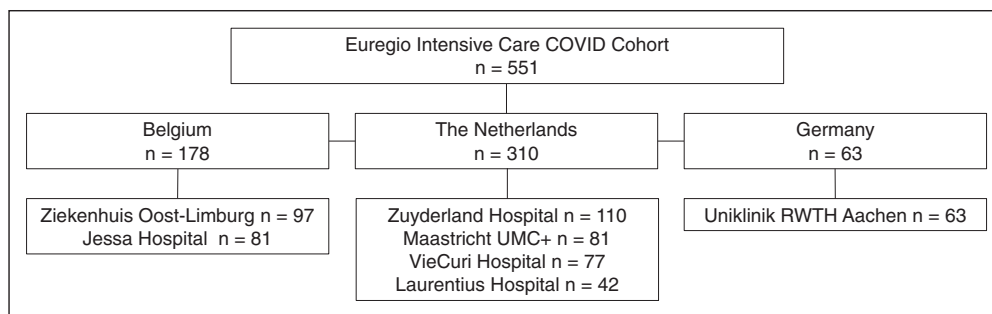
Figure 1. Flow chart. COVID = coronavirus disease, Maastricht UMC+ = Maastricht University Medical Center +, RWTH = Rheinisch Westfälische Hochschule.

Extensive information regarding participating hospitals, inclusion criteria (27), patient admission and transfer (Fig. 2*A*) (28), collected variables, project aims (22, 29), and data collection, sharing, and cleaning (30) are described in **Supplementary Digital Content 2** (http://links.lww.com/CCM/G800). Briefly, using a predefined study protocol, we collected demographic and clinical characteristics (i.e., comorbidities, hemodynamic and laboratory variables, and scores to assess disease severity), ventilation, circulatory and renal support, antimicrobial/inflammatory therapies, complications (i.e., thromboembolic events), and outcome variables (i.e., duration ICU stay, mortality). The majority of selected variables were routinely collected and

available in regular Western European Intensive Care practice, such as in the Euregio Meuse-Rhine. In this retrospective study, data were pulled from electronic medical records and collected using the study protocol, depending on the available data infrastructure of each hospital.

Ethical approval was obtained from the medical ethics committee (Medisch Ethische Toetsingscommissie 2020-1565/3 00 523) of Maastricht University Medical Center + (Maastricht UMC+). The study was performed in accordance with the General Data Protection Regulation and national data privacy laws. Based on the study protocol and ethical approval, data-sharing agreements between Maastricht UMC+ and other hospitals were drawn up by legal officers of Maastricht UMC+ and Clinical Trial Center Maastricht. Subsequently, these data-sharing agreements were judged by each participating hospital's legal department and tailored to each hospital. Investigators, heads of ICU departments, and the hospital board of
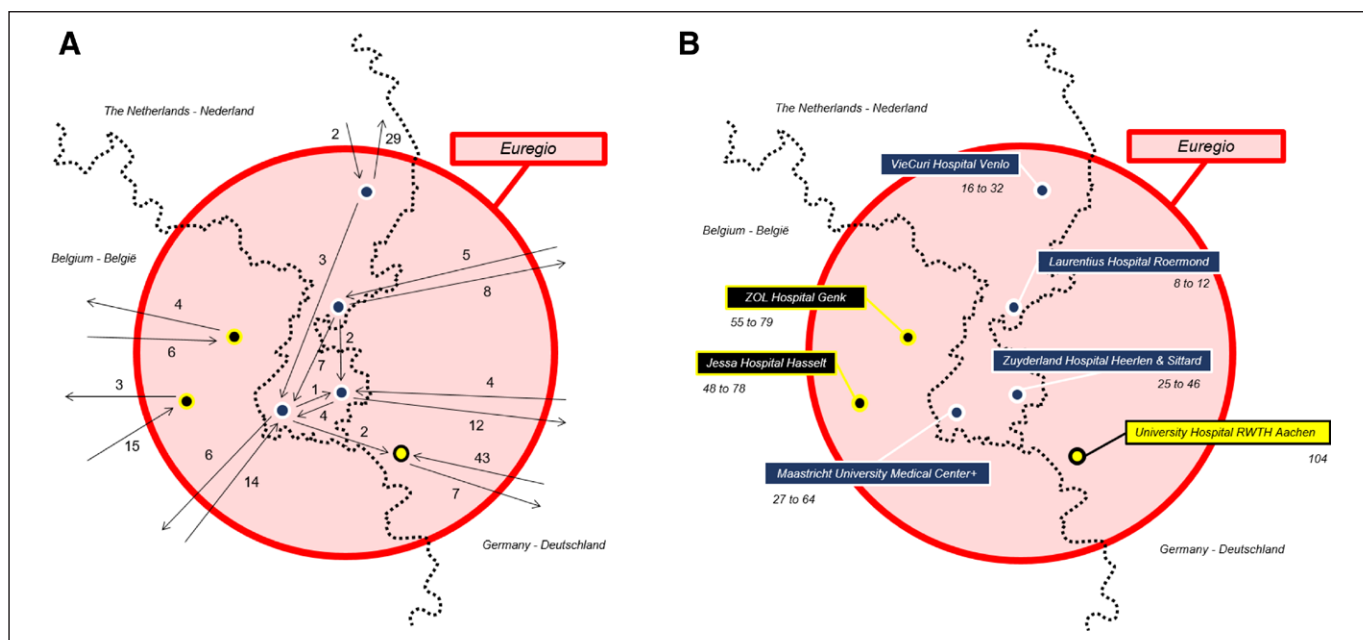
Figure 2. Patient transportation (**A**) and ICU capacity before and during the pandemic wave (**B**). **A**, The *arrows* represent the transportation of patients (exact amount displayed as number) between ICUs (displayed as *dots*) inside and outside the Euregio Meuse-Rhine (displayed as *arrows* from outside *circle* to inside and inversely). **B**, General ICU capacity compared with maximum ICU capacity during first coronavirus disease 2019 wave reported in total number of ICU beds per center (i.e., 16 to 32 means that VieCuri Hospital Venlo had 16 operational ICU beds before the pandemic, which was upgraded to 32 ICU beds due to pandemic needs). For Jessa and ZOL Hospital, the total number of beds comprises ICUs and cardiovascular care units. RWTH = Rheinisch Westfälische Hochschule, ZOL = Ziekenhuis Oost-Limburg.

directors of Maastricht UMC+ and the other hospitals then signed the final agreed data-sharing agreement.

IBM SPSS Statistics Version 25 (IBM Corporation, Armonk, NY) was used for analyses. Data are presented as mean ± SD, median (interquartile range), or percentages. The full cohort was categorized in a Belgian, Dutch, and German part of Euregio. Differences between countries were tested using one-way analysis of variance for means, Kruskal-Wallis test for medians, and chi-square for percentages, whereas Fisher exact test was used when observations within categories were low (< 5). With a random intercept for a center, mixed-effects logistic regression was used to investigate the association between Euregio country parts and ICU survival (52). To extensively challenge our hypothesis that variable healthcare system responses to a pandemic, but not disease severity, comorbidities, ICU support, therapies, and complications, determine outcome, we show six models extensively described in Supplementary Digital Content 2 (http://links.lww.com/CCM/G800). We report odds ratio (OR) with 95% CI. A two-sided *p* value of less than 0.05 was considered statistically significant.

RESULTS

From March 2, 2020, to August 12, 2020, 551 patients with COVID-19 pneumonia were admitted to seven ICUs in Western Europe (Fig. 1). Eighteen patients (3%) were transferred between two or three Euregio ICUs (Fig. 2*A*). ICU capacity in the German part was not increased during COVID-19, in contrast to the Dutch and, to a lesser extent, the Belgian part (**Fig. 2***B*).

Demographics, Disease Severity, and Comorbidities

Mean age was 65.4 ± 11.2 years, and 29% were female. Mean body mass index was 29.0 ± 5.3 kg/m² (**Table 1**). At admission, disease severity, as defined by Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, was 16.1 ± 5.5 and 6.2 ± 3.0.

Patients in the German part had more comorbidities, except for diabetes mellitus. Compared with the Belgian and German parts, fewer patients suffered from obesity, dyslipidemia, hypertension, chronic lung disease, and chronic renal disease in the Dutch part, and fewer patients smoked. APACHE II and

SOFA scores were lower in the Belgian part than the Dutch and German parts. These differences remained for the subgroup of mechanically ventilated patients (**Supplementary Digital Content 3**, http://links.lww.com/CCM/G801).

Critical Care Supportive Strategies

Ventilation Support. Seventy-nine percent of patients were supported by mechanical ventilation during ICU stay. We observed less mechanical ventilation in the Belgian part (53%) compared with the Dutch and German parts (89% and 100%, respectively) (**Table 2**). Pressure-controlled ventilation was the most applied modality in the Dutch and German parts, whereas volume-controlled ventilation was more frequently used in the Belgian part. The application of high-flow nasal oxygen was the highest in the Belgian part.

Circulatory Support. At admission, 65% of patients were supported by vasopressors. We observed less vasopressor use (39%) in the Belgian part when compared with the Dutch (74%) and German parts (97%). Accordingly, the median dose of norepinephrine was highest in the German part (0.33 µg/kg/min [0.14–0.53 µg/kg/min]). Mechanical circulatory support was highest in the German part (25%).

Renal Support. Renal replacement therapy was highest in the German part (64%) compared with the Dutch (16%) and Belgian parts (30%). Approximately half of the population on renal replacement therapy in the Belgian part was on chronic dialysis (before ICU admission), which was not present in the Dutch and German parts.

Antimicrobial/Inflammation Therapies. Almost every patient received antibacterial therapy during ICU stay (94%, 96%, and 92% for the Belgian, the Dutch, and the German parts, respectively). (Hydroxy)chloroquine was most often used in the Dutch part, with 80% of patients receiving this therapy (Table 2). In the German part, steroids were used the least (18%).

Complications. Diagnosis of pulmonary embolism during ICU stay was highest in the Dutch part (23%), whereas an imaging diagnosis of deep vein thrombosis during ICU stay was higher in the Belgian (25%) than the Dutch Euregio part.

Outcomes. In the Belgian part, the length of stay and mortality in the ICU were the lowest, compared with both Dutch and German parts (10 d [5–27 d], 14 d [7–24 d], and 33 d [20–57 d], and 22%, 42%, and

TABLE 1.
Characteristics for the Full Euregio Intensive Care Cohort and Compared Between National Euregio Parts

Characteristics	Full Cohort (*n* = 551)	Belgian Part (*n* = 178)	Dutch Part (*n* = 310)	German Part (*n* = 63)	*p*
Age, yr, mean ± SD	65.4 ± 11.2	66.4 ± 12.0	65.2 ± 10.8	64.1 ± 10.6	0.302
Female, %	29	34	25	35	0.061
Height, m, mean ± SD	1.73 ± 0.1	1.71 ± 0.10	1.75 ± 0.10	1.74 ± 0.10	< 0.001
Weight, kg, mean ± SD	87.3 ± 17.1	84.3 ± 14.8	88.0 ± 17.7	91.7 ± 18.8	0.008
Body mass index, kg/m², mean ± SD	29.0 ± 5.3	29.0 ± 5.3	28.8 ± 5.0	30.3 ± 6.2	0.096
Obesity, %	32	32	29	44	0.049
Dyslipidemia, %	27	29	24	35	0.258
Diabetes mellitus, %	26	30	24	22	0.287
Hypertension, %	47	51	40	70	< 0.001
Smoking, %	20	25	18	21	0.165
Chronic liver disease, %	1	1	1	2	0.571[a]
Chronic lung disease, %	18	20	13	41	< 0.001
Chronic renal disease, %	12	25	3	22	< 0.001
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	16.1 ± 5.5	15.0 ± 5.5	16.8 ± 5.5	15.8 ± 5.3	0.002
Sequential Organ Failure Assessment score, mean ± SD	6.2 ± 3.0	4.4 ± 2.7	7.4 ± 2.2	7.7 ± 3.2	< 0.001
Admission location, %					< 0.001
Emergency department	33	39	31	NA	
Hospital ward	50	49	61	NA	
Other ICU	16	12	8	68	

NA = not available.

[a]Fisher exact test.

Differences between national parts of Euregio were tested using the one-way analysis of variance for means, Kruskal-Wallis test for medians, and χ² for percentages unless otherwise specified. Scores were based on data of first 24 hr of ICU stay. In the German part, data at admission from the hospital ward were unavailable. The comprehensive data for the full cohort were complete, except missings for height (*n* = 27), weight (*n* = 33), body mass index (*n* = 37), obesity (*n* = 20), dyslipidemia (*n* = 108), hypertension (*n* = 1), smoking (*n* = 96), and Sequential Organ Failure Assessment score (*n* = 112).

44%, respectively [both *p* < 0.001]) (Table 2), with similar results in the subgroup of mechanically ventilated patients (**Supplementary Digital Content 4**, http://links.lww.com/CCM/G802). In crude models and after adjustment for age, sex, and APACHE II score, with a random center effect, patients in the Dutch Euregio part had an OR (95% CI) of 2.5 (1.7–3.9), and patients in the German Euregio part had an OR (95% CI) of 2.8 (1.5–5.2) for mortality, compared with patients in the Belgian Euregio part (**Table 3**, models 1 and 2). Additional adjustment for comorbidities (model 3), supportive strategies (model 4), therapies

(model 5), and complications (model 6) showed a similarly higher OR for mortality in the Dutch and German parts. This observation was similar when analyses were repeated for mechanically ventilated patients only (Table 3).

DISCUSSION

In this multinational observational cohort study of COVID-19 patients admitted to seven neighboring ICUs in the Euregio Meuse-Rhine, one region across Belgium, The Netherlands, and Germany, during the

TABLE 2.
Intensive Care Supportive Treatments and Outcomes for the Full Euregio Intensive Care Cohort and Compared Between National Euregio Parts

Variables	Full Cohort ($n = 551$)	Belgian Part ($n = 178$)	Dutch Part ($n = 310$)	German Part ($n = 63$)	p
Ventilation support					
Invasive mechanical ventilation during ICU stay, %	79	53	89	100	< 0.001
Reintubation, %	8	10	9	NA	0.042
Duration of invasive mechanical ventilation, d, median (interquartile range)	11 (2–23)	4 (0–16)	12 (5–23)	32 (18–52)	< 0.001
Admission mode of ventilation support, %					< 0.001
Pressure control	54	7	79	68	
Volume control	8	26	0	0	
Pressure support	3	0	1	22	
Continuous positive airway pressure	1	1	0	0	
Noninvasive mask ventilation	2	5	0	0	
High-flow nasal O_2	25	47	17	0	
Spontaneous/nasal O_2/other	6	13	2	10	
Unknown/missing data	1	1	1	0	
Circulatory support					
Admission vasopressor use, %	65	39	74	97	< 0.001
Admission dose of norepinephrine, µg/kg/min, median (interquartile range)	0.13 (0.08–0.24)	0.12 (0.07–0.20)	0.11 (0.07–0.18)	0.33 (0.14–0.53)	< 0.001
Mechanical circulatory support, %[a]	6	4	3	25	< 0.001
Renal support					
Renal replacement therapy including chronic dialysis, %	26	30	16	64	< 0.001
Anti-infection/inflammation therapy					
Antibacterial therapy, %	95	94	96	92	0.355[b]
Antiviral medication, %					0.009[b]
Oseltamivir	3	0	4	2	
Lopinavir/ritonavir	3	4	3	2	
Remdesivir	0.4	0.6	0	2	0.087[b]
(Hydroxy)chloroquine	57	36	80	5	< 0.001
Antifungal medication	9	6	13	NA	0.304
Steroids	31	38	30	18	0.011
Interleukin inhibitors	4	1	6	0	0.004[b]
Imaging diagnosis during ICU stay, %					
Pulmonary embolism	15	3	23	11	< 0.001
Deep venous thrombosis	10	25	4	NA	< 0.001

(*Continued*)

TABLE 2. (*Continued*).
Intensive Care Supportive Treatments and Outcomes for the Full Euregio Intensive Care Cohort and Compared Between National Euregio Parts

Variables	Full Cohort ($n = 551$)	Belgian Part ($n = 178$)	Dutch Part ($n = 310$)	German Part ($n = 63$)	p
ICU outcome					
ICU mortality, %	36	22	42	44	< 0.001
Length of ICU stay, d, median (interquartile range)	15 (6–30)	10 (5–27)	14 (7–24)	33 (20–57)	< 0.001

NA = not available.

[a]Mortality rate in extracorporeal membrane oxygenation patients was 44% for the full cohort. Differences were tested by the Kruskal-Wallis test for medians and the χ^2 for percentages unless otherwise specified. Admission corresponds to the first 24 hr of ICU stay. All patients were taken into account, implicating that treatments not received were calculated as zero. The comprehensive data for the full cohort were complete, except missings for reintubation ($n = 65$), mode of ventilation support ($n = 5$), duration of invasive mechanical ventilation ($n = 4$), admission vasopressor use ($n = 4$), admission dose of norepinephrine ($n = 61$), steroids ($n = 3$), antiviral medication ($n = 3$), interleukin inhibitors ($n = 1$), antifungal medication ($n = 185$), renal replacement therapy including chronic dialysis ($n = 4$), pulmonary embolism ($n = 3$), deep venous thrombosis ($n = 66$), and length of ICU stay ($n = 1$).

[b]Fisher exact test.

first pandemic wave, we demonstrated many similarities, but also remarkable differences in general characteristics, applied interventions, and outcomes.

The Euregio Meuse-Rhine has many similarities. In addition to similar international guidelines, healthcare standards, access to literature, and vocational training of ICU healthcare professionals (31), the general population's presumed genetic and socioeconomic background is comparable (13). We found similarities among patients (e.g., age over 60 yr, the predominance of male patients, the majority of comorbidities, and the use of antibiotics).

The differences were surprisingly more prominent. First, at baseline, patients in the German part of Euregio had more often obesity, hypertension, and chronic lung disease than patients in the Belgian and Dutch parts. In the Dutch part of Euregio, fewer patients suffered from chronic renal disease than patients in the Belgian and German parts. Second, the APACHE II and SOFA scores at admission in the Belgian part were lower, indicating a lower disease severity than in the Dutch and German parts. Third, interventions to support respiration, circulation, and renal function showed notable differences between countries. Fourth, the length of stay and ICU mortality were higher in the Dutch and German parts than in the Belgian part, and multivariable analyses for ICU mortality showed independence of age, sex, disease severity, comorbidities, support strategies, therapies, and complications.

These differences between Euregio country parts, like others (11), suggest variances in practice, referrals, and healthcare system organization, while under stress responding to a pandemic. Fifth, standard ICU capacity in the German part was sufficient, in contrast to the Dutch and Belgian parts that required expansion of ICU beds. We speculate that this has influenced care, as, for example, resource-consuming therapy such as extracorporeal membrane oxygenation was applied in the German part more often.

The relatively lower use of mechanical ventilation in the Belgian part was likely driven by admitting patients to the ICU earlier in the disease course compared with the Dutch part of Euregio. At the beginning of the pandemic, COVID-19 patients admitted to the ICU in the Dutch part were usually intubated at admission, as the potential spreading of contagious aerosols by high-flow nasal oxygen was an issue of discussion (32). For mechanical ventilation, a striking difference in ventilator settings was shown. Volume-controlled mechanical ventilation was mostly used in the Belgian part. In contrast, pressure-controlled ventilation was the number one ventilation modality in The Netherlands, as observed in our study and a ventilation study in ICUs in The Netherlands (33) and the German part of Euregio. Using a specific setting might result from specialty training interacting within a specific healthcare system. However, whether a specific ventilator setting is associated with different outcomes is unknown (34).

TABLE 3.
The Association Between Euregio Country Parts and ICU Death by Mixed-Logistic Regression Analyses

Models	Full Cohort, n = 551			Mechanically Ventilated Subcohort, n = 434		
	OR	95% CI	p	OR	95% CI	p
Model 1: crude, with random intercept for center						
Belgian part	–	–	–	–	–	–
Dutch part	2.5	1.7–3.9	< 0.001	2.0	1.2–3.5	0.008
German part	2.8	1.5–5.2	0.001	2.0	1.0–4.0	0.055
Model 2: model 1 + age, sex, Acute Physiology and Chronic Health Evaluation II score						
Belgian part	–	–	–	–	–	–
Dutch part	2.8	1.6–4.8	< 0.001	1.9	1.1–3.3	0.019
German part	3.9	1.7–8.7	0.001	2.4	1.1–4.9	0.020
Model 3: model 2 + obesity, dyslipidemia, diabetes, hypertension, smoking, chronic lung, liver, and renal disease						
Belgian part	–	–	–	–	–	–
Dutch part	3.7	1.6–8.6	0.002	2.1	1.1–3.9	0.023
German part	3.7	1.2–11.7	0.026	2.2	0.9–5.1	0.075
Model 4: model 2 + mechanical ventilation during ICU stay[a], vasopressor use at admission, mechanical circulatory support, renal replacement therapy including chronic dialysis						
Belgian part	–	–	–	–	–	–
Dutch part	2.3	1.3–4.0	0.003	3.3	1.3–8.1	0.011
German part	1.6	0.7–3.4	0.251	3.7	1.1–13.3	0.042
Model 5: model 2 + antibacterial therapy, steroids, (hydroxy)chloroquine, remdesivir, antiviral medication, interleukin inhibitors, antifungal medication						
Belgian part	–	–	–	–	–	–
Dutch part	3.3	1.7–6.1	0.001	2.8	1.3–5.8	0.007
German part	4.1	1.8–9.3	< 0.001	3.1	1.3–7.5	0.012
Model 6: model 2 + pulmonary embolism, deep vein thrombosis						
Belgian part	–	–	–	–	–	–
Dutch part	2.5	1.5–4.4	0.001	1.6	0.8–3.0	0.181
German part	3.9	1.8–8.6	0.001	2.1	0.9–4.8	0.069

OR = odds ratio.

[a]Model 4 for mechanically ventilated patients only (n = 434): the variable mechanical ventilation during ICU stay was replaced by the variable invasive ventilation duration.

p values estimated by mixed-effect logistic regression. A higher OR indicates a higher odds of ICU death between parts of Euregio, with the Belgian part as reference.

Dashes indicate the Belgian part is the reference group.

Furthermore, steroids were prescribed in 38% in the Belgian, 30% in the Dutch, and 18% in the German part. (Hydroxy)chloroquine was prescribed in 57% of the cohort, mainly driven by the 80% usage in the Dutch part of Euregio (35). The differences in the use of these antimicrobial/inflammation therapies showed that in the Dutch part, more therapies that were still under investigation were used compared, in particular, with the German part. For some of these therapies, more recent evidence shows a lack of benefit (4, 36).

In individual hospitals, ICU protocols vary, in particular those created during the first weeks of the pandemic based on both international and national guidelines (23, 35). For example, diagnostics on thrombotic events differ, as the Belgian part of Euregio used leg ultrasound, and the Dutch part used CT pulmonary angiography. Each healthcare system might have interacted differently with the fast-growing number of published studies and the rapidly succeeding disease insights (3, 4, 7, 29, 37). The similarities in treatment protocols between countries might grow as evidence from more extensive studies is implemented and recommended by international guidelines.

Furthermore, heterogeneity is partly explained by the different settings. In the German part of Euregio, only one hospital joined, and as a university hospital, the severity of patients' disease and the need for mechanical support might hamper generalizability to other German hospitals. In the Belgian part, two general hospitals were included, whereas the Dutch part included three general hospitals and a university hospital. Nevertheless, as we included all COVID-19 ICU patients admitted to our seven hospitals within a short period, had a prespecified data collection protocol using readily available data in Western European ICUs, and performed multivariable analyses, our results have a high internal validity and generalizability for Euregio. However, when comparing countries, external validity cannot be assumed, as the seven hospitals cannot represent each of their countries as a whole. Briefly, reported data of Euregio country parts on sex, age, disease severity, comorbidities, support strategies, therapies, complications, and outcomes reveal some differences but appear largely comparable with each parent nation (8, 33, 38) (www.stichting-nice.nl) and other nations (5, 6, 11, 19, 37, 39) (for extensive information, see Supplementary Digital Content 1, http://links.lww.com/CCM/G799).

Despite numerous studies among countries on the organization of Intensive Care Medicine during the COVID-19 pandemic were published (3–10), healthcare systems could not be compared directly based on their results. Our study underscores previous evidence that regional population variation might be unnoticed when evaluating data on a national level only (25, 40–42), whereas drivers of regional variation affect the risk and outcome of patients, independent of age, sex, disease severity, comorbidities, critical care support strategies, therapies, and complications (43–45). The differences observed in our cohort foster discussion about admission criteria and the interpretation of available evidence as resembled in the differences in organ support therapy.

Our study has several limitations. First, our study was not designed to compare ICU COVID-19 care outcomes between nations (5–7), although our Euregio has the unique advantage to compare healthcare systems within one region, the hospitals included in this study are only a proxy for their national healthcare system, which hampers generalizability to other hospitals in that individual country. However, this is instead more a source of heterogeneity than a limitation. Second, the number of variables for the current study is limited, as we aimed to collect mainly routinely available patient data. In particular, more extensive data on the population (e.g., race and ethnicity) were not available, which is a limitation. Third, the included patients are a selection of patients admitted to the hospital. We have no data on whether certain patients were not referred for care to the ICU and whether decisions to forgo life-sustaining treatment during ICU admission were installed (46). Nevertheless, our multivariable analyses taking dependency within centers into account show that differences in ICU outcome between Euregio parts remain after adjustments for age, sex, disease severity, comorbidities, support strategies, therapies, and complications. This suggests that other healthcare system factors (among them ICU admission criteria or end-of-life practices, for example) play a role.

CONCLUSIONS

Despite many similarities, this observational cohort study shows that admission (20, 21, 47), organ support, treatment (23, 24, 48), and outcomes (17, 22) of COVID-19 patients at the ICU strikingly differ within

the Euregio Meuse-Rhine. These differences are likely related to variances in healthcare systems, particularly ICU capacity, with each country responding differently to the rapidly evolving pandemic (11, 25, 26). To compare study outcomes and generalize these results to individual hospitals, caregivers should be aware of the possible differences. In-depth studies of the differences in protocol alignment, healthcare practice, guidelines (14), and trust in regional collaboration between healthcare systems (49, 50) are necessary to improve care for critically ill patients, also beyond COVID-19 (51).

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