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External Validation of the 4C Mortality Score and the qSOFA for Different Variants of Concern of SARS-CoV-2 Using Data of the NAPKON Cross-Sectoral Cohort Platform (SUEP)

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Background

Numerous **predictive clinical scores** with varying discriminatory performance have been developed in the context of the current coronavirus disease 2019 (COVID-19) pandemic [1]. A broad validation of these scores is essential to support clinical application. We test the transferability of two frequently applied scores, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC)'s **4C mortality score** (4C score) [2] and the non COVID-19 specific quick sequential organ failure assessment score (**qSOFA**). Both were **externally validated** using the German prospective Cross-Sectoral Platform (SUEP) of the **National Pandemic Cohort Network (NAPKON)** [3]. Our project aims to compare the utility of these two scores, stratified for the most prevalent variants of concern (VOCs) of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in Germany.

Methods

A total of 685 adults with polymerase chain reaction (PCR)-detected SARS-CoV-2 infection were included. Patients were recruited from 11/2020 to 03/2022 at 34 university and non-university hospitals across Germany. Missing values were complemented using multiple imputation. Predictive performance for all-cause **in-hospital mortality** at day of baseline visit was determined by area under the curve (AUC) with 95%-confidence interval (CI) stratified by VOCs of SARS-CoV-2 (alpha, delta, omicron) (Figure 1).

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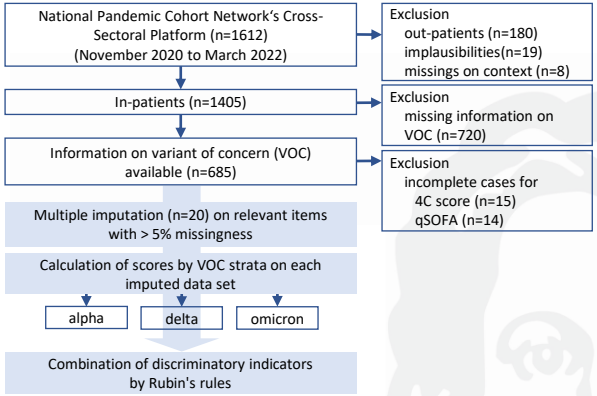

Figure 1: Study flow chart with inclusion criteria and methodological workflow.

Table 1: Discriminatory performance of the 4C Mortality Score and the qSOFA score stratified by the VOCs of SARS-CoV-2.

	Mortality % (No.)	**4C score** AUC (95%-CI)	**qSOFA** AUC (95%-CI)
All	5.4 (37/685)	0.81 (0.74-0.89)	0.57 (0.47-0.67)
Variant of concern			
Alpha	5.8 (17/294)	0.86 (0.75-0.97)	0.60 (0.45-0.75)
Delta	5.1 (18/356)	0.77 (0.66-0.88)	0.57 (0.42-0.72)
Omicron	5.7 (2/35)	0.87 (0.72-1.00)	0.60 (0.53-0.67)

Results

The analysis suggests a **high predictive performance of the 4C score** for in-hospital mortality (Table 1). This applies **for the overall cohort** (AUC 0.81 (95%-CI 0.74-0.89)) **as well as the VOC-strata** (alpha: AUC 0.86 (95%-CI 0.75-0.97); delta: AUC 0.77 (95%-CI 0.66-0.88); omicron: AUC 0.87 (95%-CI 0.72-1.00)). The overall mortality rates across the defined 4C score risk groups are 0.3% (low), 3.2% (intermediate), 11.6% (high), and 49.5% (very high). The 4C score performs significantly better than the qSOFA (Chi^2-test: p=0.001) and the qSOFA does not seem to be a suitable tool in this context.

Conclusion

Despite its development in the early phase of the pandemic and improved treatment, external validation of the 4C score in NAPKON-SUEP indicates a high predictive performance for in-hospital mortality across all VOCs. **The 4C score appears to be of high utility in Germany.** Since the qSOFA was not specifically designed for this predictive issue, it shows lower discriminatory performance, as in other validation studies [4,5]. Any interpretations regarding the omicron stratum are limited due to the sample size.

References

1. Wynants L, van Calster B, Collins GS et al. (2020): Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. In: *BMJ* 369, m1328. DOI: 10.1136/bmj.m1328.
2. Knight SR, Ho A, Pius R et al. (2020): Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Character-isation Protocol: development and validation of the 4C Mortality Score. In: *BMJ* 370, m3339. DOI: 10.1136/bmj.m3339.
3. Schons M, Pilgram L, Reese JP et al. (2022): The German National Pandemic Cohort Network (NAPKON): rationale, study design and baseline characteristics. In: *Eur. J. Epidemiol.* 37 (8), DOI: 10.1007/s10654-022-00896-z.
4. Ocho K, Hagiya H, Hasegawa K et al. (2022): Clinical Utility of 4C Mortality Scores among Japanese COVID-19 Patients: A Multicenter Study. In: *J. Clin. Med.* 11 (821), DOI: 10.3390/jcm11030821.
5. Bradley P, Frost F, Tharmaratnam K et al. (2020): Utility of estab-lished prognostic scores in COVID-19 hospital admissions: multi-centre prospective evaluation of CURB-65, NEWS2 and qSOFA. In: *BMJ Open Resp Res* 7:e000729, DOI:10.1136/ bmjresp-2020-000729.