The mean **IMX-SEV-3b score** of the 29-gene host response classifier was **significantly lower** (0.58) in **survivors** compared to **non-survivors (0.66)** in **ICU** patients with **COVID-19**

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A Transcriptomic Severity Classifier IMX-SEV-3b to Predict Mortality in Intensive Care Unit Patients with COVID-19: A Prospective Observational Pilot Study

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INTRODUCTION

The prediction of disease outcomes in COVID-19 patients in the ICU is of critical importance, and the examination of **host gene expressions** is a promising tool. The **29-host mRNA Inflam-matix-Severity-3b (IMX-SEV-3b) classifier h**as been reported to predict mortality in **emergency department COVID-19 patients** and **surgical ICU patients**. The accuracy of the IMX-SEV-3b in predicting mortality in COVID-19 patients admitted to the ICU is yet **unknown.**

OBJECTIVES

Our aim was to investigate the accuracy of the IMX-SEV-3b in predicting the ICU mortality of COVID-19 patients. In addition, we assessed the predictive performance of routinely measured biomarkers and the Sequential Organ Failure Assessment (SOFA) score as well.

METHODS

- This was a prospective observational study enrolling COVID-19 patients who received mechanical ventilation on the ICU of the Erasmus MC, the Netherlands.
- The IMX-SEV-3b scores were generated by amplifying 29 host response genes from peripheral blood collected in PAXgene® Blood RNA tubes.
- A **severity score** was provided, ranging from **0 to 1** for increasing disease severity.
- The **primary outcome** was the accuracy of the IMX-SEV-3b in predicting ICU mortality, and we calculated **the AUROC** of **the IMX-SEV-3b score**, the biomarkers CRP, D-dimer, ferritin, leukocyte count, IL-6, LDH, neutrophil-to-lymphocyte ratio, procalcitonin and the SOFA score.

CONCLUSIONS

In this observational pilot study, the mean IMX-SEV-3b score of the 29-gene host response classifier was significantly **lower (0.58) in survivors** compared **to non-survivors (0.66).** The AUROCs of the IMX-SEV-3b and the assessed biomarkers **failed to achieve statistical significance** in **predicting mortality** within this COVID-19 patient cohort, in contrast to the **SOFA score**, which did exhibit statistical significance. **Further prospective studies** are required to test the IMX-SEV-3b classifier in the ICU.

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RESULTS

A total of **53 patients** were included between **1 March and 30 April 2020,** with 47 of them being included within 72 h of their admission to the ICU. Of these, **18 (34%) patients died** during their ICU stay, and the IMX-SEV-3b scores were significantly higher in non-survivors compared to survivors **(0.65 versus 0.57, p = 0.05) (table 1).** The AUROC for prediction of ICU mortality by the IMX-SEV-3b was 0.65 (0.48–0.82) **(table 2).** The AUROCs of the biomarkers ranged from 0.52 to 0.66, and the SOFA score had an AUROC of 0.81 (0.69–0.93). The AUROC of the pooled biomarkers CRP, D-dimer, ferritin, leukocyte count, IL-6, LDH, NLR and PCT for prediction of ICU mortality was 0.81 (IQR 0.69–0.93). The specificity of the 'rule-in' Very High, High and Moderate interpretation bands was, respectively, 100%, 94% and 74%, and the sensitivity of the 'rule-out' Very Low and Low interpretation bands was 100% and 56% **(table 3).**

Table 2. AUROCs of biomarkers, SOFA and IMX-SEV-3b.

Test/biomarker/clinical score	AUROC (95% CI)
CRP (mg/L)	0.52 (0.34-0.70)
D-dimer (mg/L)	0.62 (0.45-0.79)
Ferritin (mg/L)	0.58 (0.42-0.75)
Leukocyte count (x10^9/L)	0.66 (0.48-0.83)
IL-6 (pg/mL)	0.58 (0.40-0.76)
LDH (U/L)	0.56 (0.37-0.74)
NLR	0.60 (0.43-0.78)
PCT (ng/mL)	0.59 (0.43-0.76)
IMX-SEV-3b	0.65 (0.48-0.82)
SOFA score	0.81 (0.69-0.93)
Pooled biomarker model	0.81 (0.69-0.93)

CRP: c-reactive protein. IL-6: interleukin-6; LDH: lactate dehydrogenase. NLR: neutrophil to lymphocyte ratio; PCT: procalcitonin. SOFA: sequential organ failure assessment. The pooled biomarker model included the biomarkers CRP, D-dimer, Ferritin, Leukocyte count, IL-6, LDH, NLR and PCT.

Table 1. Biomarkers, SOFA and IMX-SEV-3b scores at inclusion.

Characteristics	All Patients	Survivors	Non-Survivors	*p*-Value
	n = 53	n = 35	n = 18	
CRP (mg/L)	277 (178–345)	304 (174–341)	210 (178–347)	0.74
D-dimer (mg/L)	2.48 (1.38–5.22)	2.42 (1.18–3.96)	3.86 (1.81–8.47)	0.17
Ferritin (mg/L)	1580 (974–2680)	1660 (1130–2730)	1300 (989–2240)	0.33
Leukocyte count ($\times 10^9$/L)	8.74 (6.53–10.7)	8.31 (6.47–9.53)	10.30 (7.57–12.30)	0.06
IL-6 (pg/mL)	161 (88–307)	143 (91.5–246)	197 (87.3–395)	0.36
LDH (U/L)	322 (271–394)	320 (264–360)	341 (293–456)	0.06
NLR	7.45 (4.78–10.7)	6.72 (4.69–9.92)	8.85 (5.03–12.40)	0.22
PCT (ng/mL)	0.97 (0.470–2.70)	0.77 (0.36–2.04)	1.44 (0.90–3.20)	0.28
SOFA score	7.00 (6.00–10.00)	7.00 (6.00–8.00)	11.00 (9.00–11.00)	<0.001
IMX-SEV-3b score *	0.582 ± 0.13	0.575 ± 0.11	0.660 ± 0.15	0.050

CRP: C-reactive protein. LDH: lactate dehydrogenase. IL-6: interleukin-6. NLR: neutrophil-to-lymphocyte ratio. PCT: procalcitonin. SOFA: Sequential Organ Failure Assessment. * Mean ± SD; all others are reported as median (IQR).

Table 3. Performance of the IMX-SEV-3b in predicting ICU mortality.

IMX-SEV-3b Severity Score		Survival Status		IMX-SEV-3b Performance per Band			
		Survivor	Non-Survivor	% Patients in Band	Sensitivity	Specificity	Likelihood Ratio
IMX-SEV-3b category	Very High	0	4	8%	22%	100%	Inf.
	High	2	0	4%	0%	94%	0.00
	Moderate	9	6	28%	33%	74%	1.30
	Low	23	8	58%	56%	66%	0.68
	Very Low	1	0	2%	100%	3%	0.00

Inf: infinite.