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LETTER

Effects of delayed consent on patient characteristics in adult patients with sepsis

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Dear Editor,

Obtaining the patient's informed consent is a fundamental ethical prerequisite for clinical trials. However, sepsis patients frequently lose their ability to give informed consent. The short inclusion windows in emergency care usually render it impossible to designate and inform a legal representative in time. Therefore, the concept of a "deferred consent" has been introduced [1], albeit some investigators argue this might violate the patient's right to participate of their own free will. Consequently, state authorities and ethical boards may insist on restricting research to patients capable of giving informed consent [2].

As we were confronted with this issue when designing the IMMUNOSEP-trial (ClinicalTrials.gov-ID NCT04990232), we aimed to describe patients' characteristics and outcome depending on the informed consent process in a post hoc analysis, hypothesizing that patients with sepsis able to consent differ from those that are not. We conducted a post hoc analysis of the randomized multicenter trials MAXSEP, SISPCT, and CandiSep, all with interventions not affecting mortality [3–5]. The informed consent process is outlined in supplementary table 1.

SISPCT (1089 patients), MAXSEP (550 patients), and CandiSep (342 patients) contributed to a total of 1981 analyzed patients. Of these, 1574 (79.5%) patients were unable to give consent, while 407 (20.5%) patients gave consent themselves. Patients unable to give informed consent were either enrolled by obtaining consent from a legal representative ($n=259$, 16.5%) or by a deferred consent process ($n=1315$, 83.5%). Of the 16,105 patients assessed for eligibility, 568 patients (3.5%) were excluded as informed consent could not be obtained. Baseline characteristics stratified by status of consent are reported in supplementary table 2. Pneumonia and intraabdominal infections were the most frequent underlying infections, with pneumonia occurring more often in the "unable" and urogenital infection more often in the "able" group. Patients unable to give informed consent had higher lactate concentrations and were more likely on mechanical ventilation and vasopressor support as also reflected in higher Sequential Organ Failure Assessment (SOFA) scores. Mortality was significantly higher in the "unable" compared to the "able" group (Fig. 1), albeit "renal replacement-free days" were paradoxically and unexpectedly lower in those able to give consent.

The pooled data from these multicenter trials show marked differences in outcome depending on the ability to give informed consent. Thus, enrollment of critically ill patients into trials remains an ethical challenge where validity of the results needs to be weighed against patient autonomy. The European Union (EU) regulation No 536/2014 allows to enroll patients without informed consent in emergency situations. This, however, inflicts additional challenges as informed consent needs to be obtained later. In this case, a legal representative has to stand for the patient's presumed will or the patient consents after regaining the appropriate mental ability, which is impossible in case of early death. Results would be heavily biased when study participation depends on time to death. As an alternative, restricting enrollment

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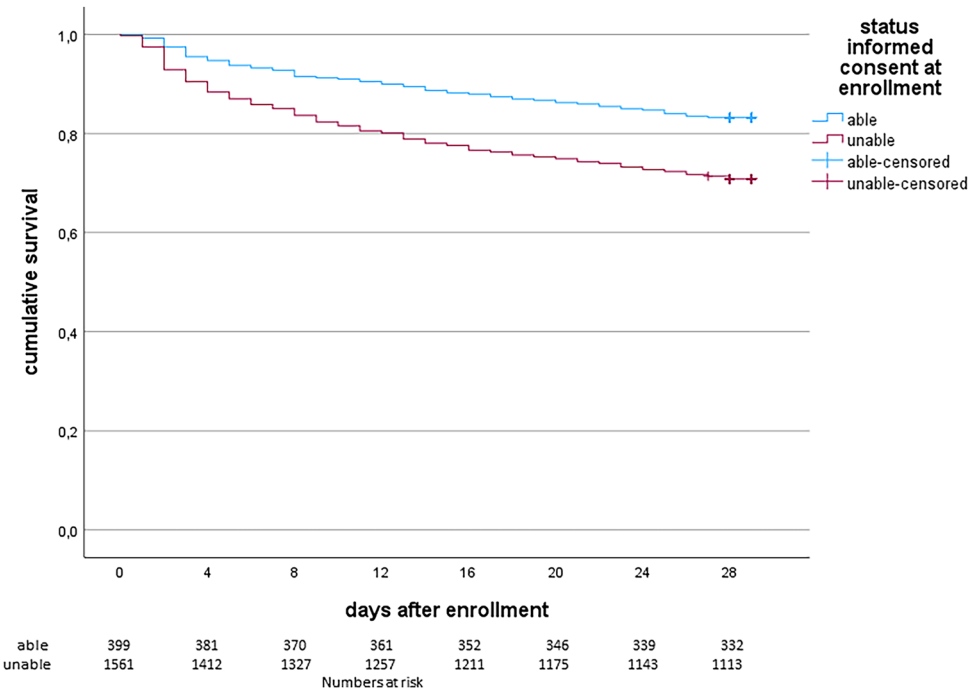

Fig. 1 Kaplan–Meier curve for survival within 28 days after study inclusion stratified by the ability to give informed consent. Log-rank test: $p < 0.001$

to patients able to give informed consent would fully preserve patient autonomy, but would severely affect external validity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-024-07718-8.

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Data availability

Data availability is settled by the original trials mentioned in references [3–5].

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