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LETTER

Modulators of systemic inflammatory response syndrome presence in patients admitted to intensive care units with acute infection: a Bayesian network approach

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Dear Editor,

Several factors may modulate the presence of systemic inflammatory response syndrome (SIRS) in patients with infection [1], which are expected to interact. Establishing a direct causal pathway among them may be challenging, and traditional statistical modeling may fail to correct (or overcorrect) for confounders. We hypothesized that some of these factors, namely age, sex, ECOG performance status (PS) [2], source of infection and presence of diabetes and active cancer, could modulate the presence of SIRS at intensive care unit (ICU) admission. We expected that increasing age, diabetes, female gender, worse performance status and cancer would be associated with lower SIRS probability and that some specific infection sources (such as bloodstream infection) would be associated with higher SIRS probability.

Of 129,680 patients, 27,438 (21.1%) admitted to 93 ICUs because of infection between 2014 and 2015 were elected for this analysis [2]. Mean age was 67 ± 20.4 years and median Sequential Organ Failure Score (SOFA) score was 3 (interquartile range, 1–6) points. The main sources of infections were respiratory (38.4%), urinary (14.3%), soft tissue (4.7%) and abdomen (4.4%). Patients' data are shown in the electronic supplementary file (ESM sTable 1) together with detailed methods for SIRS calculation and missing values. At least two SIRS criteria were present in 14,548 (53%) patients. We elaborated a directed acyclic graphic (DAG) considering the beforementioned variables and organ failure [4]. The minimal sufficient adjustment set for estimating the direct effect of a predictor on SIRS was defined to remove potential backdoor pathways without opening inappropriate pathways (such as adjusting for colliders). We queried the DAG using a Bayesian network model and by applying logistic regression adjusted as suggested by the DAG [4]. One model was built for each predictor possibly associated with outcome (SIRS). We used R with packages *bnlearn* and *DAGitty* [3, 4].

The resulting DAG is shown in Fig. 1a; a detailed explanation of reasons for choosing each arch in the DAG is discussed in the ESM. Age, DM, performance status, cancer, source of infection and sex were all considered to be related to SIRS in the DAG. After adjusting for DAG-specified variables, age (odds ratio, OR 0.90; 95% confidence interval, CI 0.89–0.91, for 10-year increment), cancer (OR 1.40; 95% CI 1.31–1.50), performance status (OR 1.21; 95% CI 1.14–1.29 for moderate impairment and OR 1.26; 95% CI 1.18–1.36 for severe impairment) and infection source (see sTable 2 in ESM for details) were associated with SIRS. Predicted probability of SIRS using the Bayesian network model for older (> 65-year-old) vs. younger (≤ 65-year-old) patients stratified by source is shown in Fig. 1b. The severity of organ dysfunctions measured by SOFA [5] was a collider. Other examples are given in the ESM together with their clinical implications.

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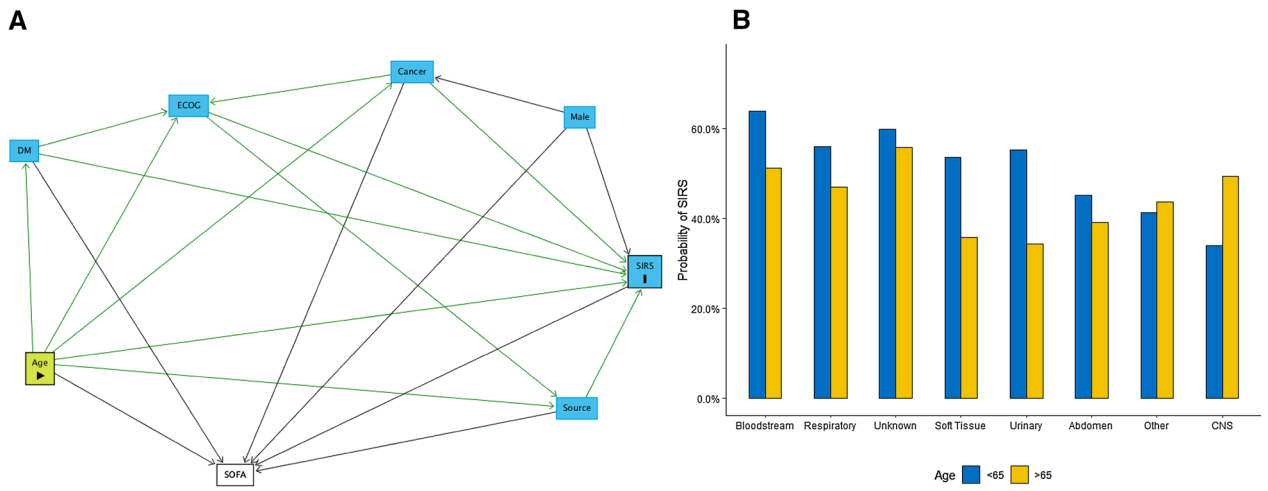

Fig. 1 **a** Directed acyclic graph (DAG) for the study. Green arrows represent potential causal pathways between variables. The elected outcome variable was presence of SIRS (blue). Age, the variable of interest, is shown in the yellow box. Dark arrows show the paths not related to the association between age and SIRS, including organ failure (measured by SOFA score [5]). *ECOG* Eastern Cooperative Oncology Group Performance Status Scale, *DM* diabetes mellitus. **b** Predicted probability of SIRS using conditional probabilities from a Bayesian network using the DAG (shown in **a**) according to sepsis source (*x* axis) and age (dichotomized at 65 years for clarity). The graph shows a clear interaction among infection source, age and presence of SIRS

The present work has both methodologic and clinical implications. First, it highlights the complexity of building regression models in a scenario with several variables and how DAG can help visualizing associations. From a clinical point of view, these results call for judicious use of SIRS criteria as a screening tool for severe infection in elderly patients and in those with a specific infection source. Therefore, it is conceivable that overall the performance of the SIRS criteria as a screening tool may be different depending on the population, its risk factors and age, among other confounders.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05595-0) contains supplementary material, which is available to authorized users.

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Author contributions
FGZ, FJA and MS participated in study conception, data interpretation and drafting of the manuscript. FGZ and FJA performed the statistical analysis and produced the figures. FGZ, FAB, JIFS and MS led data collection and cleaning. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

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Compliance with ethical standards

Conflicts of interest
JIFS and MS are founders and proprietors of Epimed®, a cloud-based solution for ICU performance measurements and benchmarking. The other authors report no conflicts of interest to declare.

Ethical approval
The local ethics committee at the D'Or Institute for Research and Education (Approval Number 334.835) and the Brazilian National Ethics Committee (CAAE 19687113.8.1001.5249) approved the ORCHESTRA study and analyses.

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