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LETTER TO THE EDITOR

TITLE:

THE ROLE OF ETHICAL ATTITUDES ON MORTALITY OF PATIENTS WITH DISORDERS OF CONSCIOUSNESS

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Decision-making on disorders of consciousness (DoC) still represents a critical dilemma. In most cases, families and physicians are burdened with a decision on end-of-life issues without having valuable information on chances of recovery and survival<sup>1</sup>.

In the article that recently appeared in this journal, Estraneo and coauthors<sup>2</sup> present a prospective analysis of two-year mortality risks of a cohort of DoC patients. The results suggest that older age and lower CRS-R scores are risk factors for mortality in patients with Unresponsive Wakefulness Syndrome (UWS). In contrast, female sex and the absence of alpha rhythm on EEG are associated with higher mortality risk in the Minimal Conscious State (MCS) group.

The authors argue that this evidence could guide the decision-making of clinicians and families and promote international standardization of prognostic procedures for patients with DoC.

We want to focus here on the possible obstacles in searching for independent risk factors for mortality in this particular population of patients.

Firstly, the study cohort includes patients with DoC of recent onset, enrolled in different clinical settings: intensive care units (ICUs), rehabilitation units (almost 80%) and neurology departments. However, the sample recruitment excluded subjects with organ dysfunction or unstable clinical condition, such as hemodynamic instability or severe respiratory failure. These characteristics make the study sample particular and unrepresentative of all the patients with DoC in the first three months of the clinical course, especially those admitted to an ICU.

Moreover, the early stability of these patients at entry suggests that any subsequent event, which the study could not analyze, might have had a critical role in mortality. Therefore, there is no information on the putative variables that affected the "natural clinical history of patients with DoC" recruited into the study.

The occurrence of disease complications is a critical factor in survival in DoC patients, either for the uncertain outcome of the treatment or because it triggers the decision-making process on treatment limitation (TL), such as withholding or withdrawing a life-sustaining therapy<sup>3</sup>.

Emergencies requiring resuscitation, decisions on mechanical ventilation and tracheostomy, artificial nutrition or antibiotics are among the most frequent circumstances that open a "window of opportunity for death"<sup>4</sup>, a critical period in which fundamental choices on survival-prolonging treatments must be taken.

The timing and frequency of TL across the three continents and even across countries are different, with a clear North-South gradient<sup>5</sup>.

In North America has been reported a "time pressure" to withdraw life-sustaining therapies before it becomes unnecessary. The pressure stems from the fear that once passed the critical moment, the patient will be bound to unacceptably poor quality of life. Consequently, many patients are letting die without waiting for more precise prognostic information<sup>4, 6</sup>. Especially when considering ICUs, TL lead to the death of about 70% of Traumatic Brain Injury (TBI) patients, mainly in the first three days of admission<sup>7</sup>.

In Europe, very distant ideological stances coexist. For example, the Royal Dutch Medical Association (KNMG) has stated that a physician is expected to discontinue life-prolonging treatment when the patient has a poor prognosis of regaining consciousness. This assertion is based on the societal feeling that the perpetuation of the patient's status would be contrary to human

dignity<sup>8</sup>. Consequently, for decades more than 50% of Dutch patients in a UWS/Vs have died from comorbidity after a nontreatment decision or withdrawal of artificial nutrition and hydration<sup>9</sup>.

Central and South European Countries present opposite scenarios. In Austria, for example, the "Austrian Coma Society" (Osterreichische Wachkoma Gesellschaft) stated that "VS (Vegetative State) is considered to be one of the severest neurological conditions, and the patients have the right to live a valuable life with all needed treatments"<sup>10</sup>.

In Italy, legal regulation of the TL went into effect in January 2018, so all Italian patients recruited in clinical studies had the chance to access this option before this date. Concerning the critically ill patients, Do Not Resuscitate/Do Not Intubate orders are significantly more frequently applied in North Europe than in South Europe<sup>11</sup>, with a consequent higher rate of long-term mechanical ventilation use<sup>12</sup>. Besides the cultural background, economics and ethics, also religion plays a role in end-of-life decisions. An international survey involving doctors, patients and families in ICUs<sup>13</sup> showed that religious respondents are more likely to adopt life-sustaining therapies such as cardio-pulmonary resuscitation and ventilator treatment than people "affiliated" to a religion.

As a consequence of these differences, in some Countries, TL are limited to rare situations, whereas in other cases represent the most frequent cause of death in the acute phase, as also shown by the prevalence of UWS/Vs patients across Countries<sup>14</sup>.

Referring to Estraneo's paper, the cohort of patients was homogeneous for clinical stability and disease duration at the time of the recruitment. However, in the following two years, the availability of resources and propensity to treatment and survival necessarily varied according to the Country of recruitment. Hence, for example, a patient admitted to an ICU in the US might have a completely different course than a patient hospitalized for several months in a rehabilitation centre in Italy.

Consequently, we wonder whether female sex, alpha rhythm, older age and CRS-R score might be reasonably considered independent risk factors for mortality in this cohort of patients with DoC.

In our view, survival analyses on severely ill patients, such as those with DoC, should consider the impact of the TL utilization from the onset of the disease to the end of the follow-up without underestimating the ethical attitudes, religious and other countries-specific factors.

Only by giving full consideration to all the factors that could influence the natural history of DoC, we could collect valuable and generalizable prognostic information, which would support the families' and doctors' decision-making process and improve the care offered to these frail patients.

## DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no financial or other conflicts of interest.

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