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Prediction of Three-Month Mortality in Patients Undergoing Mechanical Ventilation

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Abstract

An elevated red blood cell distribution width (RDW >15%) predicts poor prognosis in various disease states. We assessed whether this also applies to patients undergoing prolonged mechanical ventilation.
***Aim:** To compare the physicians' intuition of poor short-time prognosis, RDW >15%, RDW/Hb >1.4 with three-month mortality of patients treated with prolonged mechanical ventilation.*
***Design:** Prospective observational study*
***Subjects:** Patients hospitalized for prolonged mechanical ventilation*
***Method:** Three physicians (MD1,2,3) independently intuited the patients' prognosis. An outside observer extracted RDW values from the patient records and computed the RDW/hemoglobin ratio (RDW/Hb).*
***Results:** Two patients died during the three-months study period, yet a poor short-term prognosis was intuited by MD1 in 12/66 patients, by MD2 in 12/34 patients, and by MD3 in 3/32 patients. RDW >15% was found in 22 patients and RDW/Hb >1.4 in 33 patients.*
***Conclusions:** The physicians' intuition of poor prognosis in long-term survivors of mechanical ventilation was deceptive, as were RDW >15% and RDW/Hb >1.4. This data contrasts with reports about the significant prognostic information provided by RDW >15% in a variety of diseases.*

***Keywords:** mechanical ventilation, red blood cell distribution width, prognosis.*

Introduction

Clinician prediction of survival is a challenging task (1). To date, clinician prediction of survival remains the most practical and most commonly used approach to estimate prognosis. It is a subjective estimate based on clinical experience and knowledge of prognostic factors and the natural history of disease (2). In this approach, the clinician is asked "How long do you think the patient will live?" and a temporal answer is provided. The temporal prediction has a number of advantages over existing prognostic models, including its convenience and quick response. However, the prediction is highly clinician dependent, making it less reliable (3,4). The clinician's intuition may be stimulated by other questions: Would you be surprised if this patient died in a specific time frame? What is the probability of survival of this patient in a specific time frame? (1). The tendency to overestimate survival in answering to how long will this patient live has been well established (5-7). At a difference to the former, the surprise question may improve prognostic accuracy. Indeed, the surprise question - would you be surprised if this patient died in a specific time frame? - performs relatively well as a survival prediction tool, with a C-index of 0.75 in a meta-analysis of studies in the oncology setting. Interestingly, accuracy of the surprise question may be higher in oncology patients than in other disease groups (8,9). Probabilistic estimates may outperform the temporal approach, as demonstrated by a systematic review of 42 studies (5). Clinical signs and symptoms may improve the accuracy of prediction of survival, the most significant of which include deterioration in performance status (10). Yet, patients with serious illnesses characterized by end-stage organ disease can live for years and can experience unpredictable acute

events. Prognostic uncertainty decreases clinician confidence in communicating prognosis with patients (11). An elevated red blood cell distribution width (RDW >15%) predicts poor prognosis in various disease states. We assessed whether this also applies to patients undergoing prolonged mechanical ventilation. Recent studies have shown that an elevated red blood cell distribution width (RDW) may help in assessment of disease severity and in prognostication of patient survival (12-23, 9-20). The red blood cell distribution width (RDW) is a simple measure of red blood cell size heterogeneity (i.e., anisocytosis), that is calculated by dividing the standard deviation of erythrocyte volumes by the mean corpuscular volume. Higher RDW reflects greater variability in RBC size, indicating dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes. An increased RDW mirrors a profound disregulation of erythrocyte homeostasis under pathologic conditions: oxidative stress, inflammation, poor nutritional status, and alteration of erythropoietin function (24-26). Traditionally, the RDW has been used in the diagnosis of anemias. Recently, there is increasing awareness of an association between elevated RDW occurring independently of anemia in several disease states, with inherently increased morbidity and mortality. This association has been reported in cardiovascular diseases, venous thromboembolism, cancer, hematologic malignancies, diabetes mellitus, rheumatic disorders, community-acquired pneumonia, chronic obstructive pulmonary disease, liver and kidney failure, sepsis, and critical illness (13-23). It appears that elevated RDW might bridge the relationship between inflammation and tumorigenesis (23). So, an elevated RDW may serve as integrative index of enhanced patient fragility, the risk of clinical deterioration, might help in assessment of disease severity and prognostication of patient survival (13-23).

Hospitalized patients undergoing prolonged mechanical ventilation have, in general, a poor long-term outcome. In one study, at one year only 9% were alive and independent of major functional status limitations (27); their outcomes were significantly worse than expected by physicians. Indeed, current indexes of illness severity are unable to assess the long-term prognosis of patients requiring prolonged mechanical ventilation (28). We wondered whether the clinical prognostic model, which uses temporal, surprise, or probabilistic questions (1,28), could be improved using the RDW? The present study was designed to address the question.

Patients and Methods

The Institutional Review Board approved this prospective observational study and waived the need for informed consent. The study was designed to compare two parameters: A. a set of hematological data at the time of study entry (RDW, RDW/Hb ratio, TSAT), and B. the physicians' estimate of the patient's prognosis, reappraised 6 weeks later. Concordance between mortality over a three months period, the prognosis intuited by different physicians, and the RDW and RDW/Hb was assessed.

Patients

Included were all residents receiving mechanical ventilation through tracheostomy conditioned by their staying in the wards for at least 6 weeks and having at least two blood counts on record.

Method

Laboratory data including the RDW, hemoglobin, iron, and transferrin were extracted from the medical records by an outside observer. The RDW/hemoglobin ratio (RDW/Hb) was calculated in which the RDW is expressed in percent and the hemoglobin in g/dL. We proposed the RDW/Hb ratio based on results of a pilot study in residents of long-term geriatric care, showing that a RDW/Hb >1.4 correlated closer with poor patient prognosis than did RDW >15% (29).

Physicians who were caring day-to-day for the patients were asked to estimate the prognoses targeted on the forthcoming 3 months. This time limit was set based on reports of high one-year mortality in patients undergoing permanent mechanical ventilation (1,28). For prognostication, objective and subjective parameters were used. The objective parameter was instability vs. stability of vital signs during the six weeks before study entry. The subjective parameter was the physicians' intuition that an unfortunate outcome might occur within 3 months. Patients who appeared clinically unstable and their physicians were intuiting nearness of an ill-fated outcome were classified "poor prognosis patients". In Department A, MD1 and MD2, intuited independently the patients' prognosis. In Department B, MD1 and MD3 intuited independently the prognoses.

Data analysis: The analysis focused on two points: First, the association of three-months mortality with poor prognosis, elevated RDW, and elevated RDW/Hb. Second, assessment of the inter-observer and intra-observer variation of prognosis at the time of study entrance and six weeks later.

Results

Included were 34 four patients receiving prolonged mechanical ventilation in Department A and 32 patients in Department B, who were suffering from severe pulmonary or neuromuscular disorders. The mean duration of mechanical ventilation before the studies begin was 32 months (range 5-83 months). The patients' characteristics and other pathologic conditions are shown in Table 1.

Patient data	Dept A (No 34)	Dept B (No 32)
Female	18	19
Age >65 years	24	25
UWS	17	14
Dementia CDR 2 or 3	7	22
Stroke	7	13
Ischemic heart disease	9	10
Heart failure NYHA 3 or 4	5	9
Stage 3 – 4 pressure ulcers	5	0
Diabetes mellitus	12	8
eGFR <30 mL	2	2
Difficult airway	5	0
Antibiotics >once/2 months	14	13
Stay in the ward - months (range)	9 - 54	5 - 83

Table 1: Patient characteristics at study entry. UWS: unresponsive wakefulness syndrome. NYHA: New York Heart Association class.

Poor prognosis on study entry was intuited by MD1 in 12/66 patients (departments A and B), by MD2 in 12/34 patients (Department A), and by MD3 in 3/32 patients (Department B). Six weeks after study entry prognostication was repeated, each physician being blinded to the earlier prognosis statement, and also to other physicians' prognoses. Inter-observer and intra-observer disparity of prognoses are shown in Table 2.

Observer	Poor prognosis study entry (No. patients)	Poor prognosis 6 weeks later (No. patients)	Poor prognosis diagnosis consistence (No. patients)
MD_1	12 (out of 66)	10 (out of 66)	7
MD_2	12 (out of 34)	9 (out of 34)	8
MD_3	3 (out of 32)	6 (out of 32)	2

Table 2: Inter-observer and intra-observer variation of prognosis

On study entry, RDW >15% was found in 12 patients out of 34 in Department A and in 10 patients out of 32 in Department B. RDW/Hb ratio >1.4 was found in 14 patients out of 34 in Department A and in 19 patients out of 32 in Department B.

Outcomes: During the 3 months follow-up one patient was weaned from mechanical ventilation. This patient was diagnosed in “stable condition” by both MD1 and MD2. The RDW 14.6% and RDW/Hb 1.27 were normal. Two patients died during the study period. One of them was diagnosed “poor prognosis patient” by MD1 and MD2. The patient's RDW was 14% (normal) while the RDW/Hb was 2.03 (highly elevated). The other patient who died qualified by MD1 as “poor prognosis patient” but not so by MD3; his RDW was 14.7 (normal), the RDW/Hb 1.66 was elevated.

Neither the clinicians' intuition nor the laboratory indices RDW >15% and RDW/Hb ratio >1.4 provided a meaningful prediction of the patients' three-month survival.

Discussion

Prognosis is disease specific, but also, the individual patient's prognosis is shaped by competing risks , mainly comorbidities. Three reviews have reported on the accuracy of clinician estimates which suggest that clinicians’ predictions about length of survival are inaccurate and unreliable (30-32). These reviews have all been limited to patients with advanced cancer. Evidence for patients with a non-cancer diagnosis suggests that clinicians’ determinations of prognosis in these patients may be more inaccurate than those in cancer patients (33). In our present study, subjects who were clinically unstable and the physicians intuited nearness of an ill-fated outcome were classified "poor prognosis patients". The three-month outcomes were better than expected. In Department A, one patient died among six who were classified by MD1 as "poor prognosis patients", and one of those twelve subjects classified by MD2 as "poor prognosis patients". In Department B, one patient died among six subjects classified by MD1 "poor prognosis patients", and none of the three designed so by MD3. Obviously, the MDs greatly exaggerated the risk of poor outcome in this patient

population. Indeed, data form the literature indicates that the existing indexes of severity-of-illness are unable to assess the long-term prognosis of patients requiring prolonged mechanical ventilation (28). In the present study, the patients being long-term survivors on mechanical ventilation might belong to the better extreme in the spectrum, even when appearing to be clinically unstable. The subjective element in prognostication was apparent also in the large inter-observer difference in classifying the subjects as "poor prognosis patients".

Also, RDW >15% and RDW/Hb ratio >1.4 were poor correlates of the three-month mortality. This differs from data in the literature, however, referring to patients essentially different from those comprised in the present study. There is sizable evidence that an elevated RDW might predict mortality on the short as well as on the long term, in various diseases and settings, in hospital and in the community (13-23,17-22, 34). Yet, prognosis is population specific. The broader the spectrum of populations, the more complex are factors affecting patient survival.

In conclusion, prediction by clinicians of the three-month mortality of patients receiving prolonged mechanical ventilation was deceiving, and the hemoglobin indices RDW >15% and RDW/Hb ratio >1.4 did not provide better indication. This data contrasts with reports concerning the significant prognostic information provided by RDW >15% in a variety of diseases, however in populations greatly different from ours. The insight provided by the present study might stipulate modesty to our expectations.

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