ACUTE LUNG INJURY IN CRITICALLY ILL PATIENTS: ACTIN-SCAVENGER *GELSOLIN* SIGNALS PROLONGED RESPIRATORY FAILURE

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ABSTRACT—**Background:** Gelsolin is an actin-scavenger controlling the tissue damage from actin in the blood. Gelsolin levels in circulation drops when tissue damage and corresponding actin release is pronounced due to catabolic conditions. The purpose of this study was to determine if low plasma gelsolin independently predicts a reduced chance of weaning from ventilator-demanding respiratory failure in critically ill patients within 28 days from admission. **Results:** This cohort study included 746 critically ill patients with ventilator-demanding respiratory failure from the randomized clinical trial, "Procalcitonin And Survival Study (PASS)." Primary end point was successful weaning from mechanical ventilation within 28 days. We used multivariable Cox regression adjusted for age, sepsis, PaO_2/FiO_2 ratio and other known and suspected predictors of persistent respiratory failure. Follow-up was complete. For medical patients, baseline-gelsolin below the 25th percentile independently predicted a 40% lower chance of successful weaning within 28 days (HR 0.60, 95% CI 0.46–0.79, $P = 0.0002$); among surgical patients this end point was not predicted. Low gelsolin levels predicted chance of being "alive and out of intensive care at day 14" for both medical and surgical patients (HR 0.69, 95% CI 0.54–0.89, $P = 0.004$). Gelsolin levels did not predict 28 day mortality for surgical or medical patients. **Conclusions:** Low levels of serum gelsolin independently predict a decreased chance of successful weaning from ventilator within 28 days among medical intensive care patients. This finding has implications for identifying patients who need individualized intervention early in intensive care course to prevent unfavorable lung prognosis in acute respiratory failure. **Trial registration:** This is a substudy to the PASS, Clinicaltrials.gov ID: NCT00271752, first registered January 1, 2006.

KEYWORDS—Baseline parameters, biomarker, ICU, mechanical ventilation, successful weaning

ABBREVIATIONS—SPD—Surfactant protein D; Q1—lower quartile; PCT—procalcitonin; sTM—soluble thrombomodulin and nitrogen; NOS3—oxide synthase type III

INTRODUCTION

Every year 5.7 million patients are admitted to ICU in the United States (1). Of these, 20%–40% requires mechanical ventilation (2). Critically ill patients with respiratory failure requiring mechanical ventilation have a high mortality rate (3, 4). To improve survival of this vulnerable group of patients, we need more knowledge about which potentially modifiable parameters, present at baseline, that influences mortality.

However useful the current acute respiratory distress syndrome (ARDS) is, many patients suffer from a certain degree of lung injury, and eventually die or suffer persistent dependence of mechanical ventilation, although they do not meet the criteria for ARDS. This prompts the need for further research to describe these patients physiologically, biochemically, and clinically, eventually to offer treatment options for this group. Biomarker research is one among several means to describe such patients.

Intracellular actin is involved in maintaining cell shape and motility (5–7). In catabolic conditions, e.g., sepsis, trauma, hepatic necrosis, ARDS, and myocardial infarction, damaged cells release globular actin to the extracellular space and the bloodstream (7, 8). The concentration of actin in the circulation may saturate the actin-scavenging proteins, gelsolin and Gc-globulin (9). This leads to accumulation of actin that polymerizes and forms actin filaments (7, 9). Actin filaments in the blood contribute to pulmonic vessel obstruction, pulmonary micro thrombi, and endothelial damage (7, 9, 10). In addition, actin activates platelets, which further increases the risk of thrombi and thereby obstruction of the microcirculation in the lungs (7, 11).

Gelsolin exists as intracellular and extracellular forms coded by the same gene on chromosome 9 (12). The extracellular gelsolin is primarily produced by muscle cells and diffuses to circulation afterward (13). Extracellular gelsolin breaks down actin filaments and forms gelsolin-actin complexes, which

leads to a decreasing concentration of free gelsolin in the bloodstream when actin increases (7, 9). Particular conditions such as sepsis, acute liver failure, myocardial infarction, lung injury, trauma and chronic inflammatory diseases are associated with lowered plasma gelsolin concentration (6, 11, 14–21). Patients with the aforementioned conditions and a low concentration of gelsolin seem to have a longer period of mechanical ventilation, longer stay at ICU and an increased mortality compared to patients with preserved gelsolin levels, albeit the sample sizes studied have been small (11, 10, 22). The plasma concentration of gelsolin in healthy individuals is measured to a wide range of values, ranging from 190 mg/L to 517 mg/L (7, 11, 23).

An already known biomarker of lung injury and activity of lung diseases is surfactant protein D (SPD), to which gelsolin could be an alternative or supplement to (24–26). Since SPD usually is found in the alveoli, an increasing serum SPD indicates damage to the alveolar epithelial barrier. An increased serum SPD predicts a longer duration of respiratory failure (24, 26). The change in soluble thrombomodulin (sTM) gives a measure of endothelial damage (27).

Objectives

The primary objective of this study was to determine whether the risk of persistent ventilator-demanding respiratory failure is increased among critically ill patients if baseline gelsolin is low, measured using the end point "successful weaning from respirator within 28 days." Secondarily, we wanted to determine if patients with a low baseline gelsolin level had a poorer overall prognosis measured as mortality and duration of stay at ICU. Additionally, as an exploratory objective, we aimed to find out whether low baseline gelsolin proceeded endothelial damage later in the patient course measured as change in the level of soluble sTM.

METHODS

Study population

This multicenter observational study was based on data collected among patients in 9 ICUs requiring mechanical ventilation within the cohort of the "Procalcitonin And Survival Study" (PASS)-trial between 2006 and 2010 (28). The patients had blood samples drawn every day until day 28 if still in ICUs. Data were collected in line with guidelines for Good Clinical Practice (29).

Patients aged 18 or above, requiring mechanical ventilation and having a measurement of serum gelsolin at day 1 were included. Patients could not be included in the study if they were pregnant, breast feeding or had an expected stay at ICU <24 h.

Sample analysis

Gelsolin was subsequently determined in blood samples from day 1.

Samples were stored at $-20°C$ until after study completion and analyzed subsequently to make sure that the physicians were blinded to the gelsolin levels during extubation of the patients. Gelsolin was measured in serum samples which were thawed at $37°C$ and mixed before analysis. An automated Modular P analyzer (Roche Diagnostics, Risch-Rotkreuz, Schweiz) was used for the determination of gelsolin with the applied settings and performance characteristics provided by the reagent manufacture (30). The concentration-dependent immunoprecipitation, formed by the mixture of Rabbit Anti Human Gelsolin (Dako Code No. A0146, Glostrup, Denmark), and gelsolin containing patient samples was measured against the calibrator material (Dako Code No. X0908, Glostrup, Denmark). Control determination was executed multiple times for each calibration and mean within calibration coefficient of variation was 2.7%. The lowest standard point on the calibration curve was 17.2 mg/L.

End-points

The primary end point was "successful weaning from respirator within 28 days of ICU admission." Only patients who were alive and extubated at day 28 were considered successfully extubated. The time point for extubation was defined as the last day the patient was receiving mechanical ventilation.

The secondary end points included 28 days mortality, alive and out of intensive care within 14 days, and change in the level of endothelial damage (defined as continuous soluble sTM concentration).

Variables—The exposure variable is plasma gelsolin at day 1 <25th percentile. The confounding variables are sepsis/septic shock (yes vs. no), surgical origin (yes vs. no), gender (male vs. female), age (per year increase), acute thrombosis defined as acute myocardial infarction, pulmonary embolism, cerebral infarction, mesenteric embolism, or medulla spinalis infarction (yes vs. no), chronic inflammatory diseases defined as rheumatoid arthritis, Sjögren syndrome, fibromyalgia, spondylosis, hepatic cirrhosis, systemic lupus erythematosus, vasculitis, and chronic glomerulonephritis (yes vs. no), baseline procalcitonin (PCT) (≥ 1 μg/L vs. <1 μg/L) (31), PaO_2/FiO_2 ratio (lower quartile (Q1) versus upper 3 quartiles (Q2–Q4)), baseline SPD >85th percentile, Apache II score (<25 vs. ≥ 25) (32) and chronic obstructive pulmonary disease (COPD). The variables were chosen because they were all known or suspected predictors of duration of ventilation or levels of baseline gelsolin.

Statistical analysis of data—We used a Cox proportional hazards model to analyze difference in time to event in-between the patients in the lower quartile and the upper 3 quartiles (e.g., death, successful extubation), and further to make an interaction analysis. We compared the number of ventilator-free days and ICU-free days within 28 days with a Mann–Whitney U test. The division into the lower quartile and the upper 3 quartiles was defined before the analysis was carried out. Cumulative incidence curves and Kaplan–Meier curves were used to illustrate events over time. Pearson's correlation analysis was used to evaluate correlations between baseline gelsolin and change in soluble sTM from day 1 to day 4. Two-sided P values were used, $P < 0.05$ were defined as significant. Statistical analyses were made in SAS 9.4 windows version Cary, NC) and IBM SPSS Statistics version 22 (Armonk, NY).

A power calculation was carried out for the primary end point prior to the study with the prior known sample size, which was 758. We later adjusted sample size to 746, because 12 patients did not have a baseline gelsolin measurement or we did not know if they had a surgical origin. A conventional limit of type 1 error was set at 0.05, the exposure variable is present in 25% of patients (lowest quartile, defined), the end point (successful weaning within 28 days) was thought to be present in 85% of the remaining patients, variance inflation factor of 0.3 and a power of (1-β) 0.8. This results in a detection limit of the odds ratio of 0.68 in a logistic regression model. Power calculation was done with "Study Size 3.0", Creostat, Frölunda, Sweden. The exposure variable is lower quartile plasma gelsolin at day 1. The end point is "successful weaning from respirator within 28 days of ICU admission."

RESULTS

In total 1,200 patients were recruited between 2006 and 2010 in "the PASS study." Of these, 746 patients were intubated at baseline and had analyzed baseline gelsolin concentration (Fig. 1). In total, 746 patients were included in the study. Baseline characteristics of the included patients are presented in Table 1.

The patients were divided into 2 groups; a lower quartile (Q1) and 3 upper quartiles (Q2–Q4) according to baseline gelsolin measurement. The median gelsolin concentration in this population was 75.1 mg/L (IQR = 50.3–105.1), in the lower quartile it was 29.1 mg/L (IQR = 17.2–42.2), whereas the median gelsolin concentration was 90.0 mg/L (IQR = 69.9–115.6) in the upper 3 quartiles.

Successful weaning from mechanical ventilation within 28 days is related to gelsolin levels at baseline

Intubated patients with a baseline gelsolin level below the 25th percentile had 29% lower chance of being successfully weaned within 28 days compared to the patients with baseline gelsolin level above the 25th percentile (HR 0.71, 95% CI
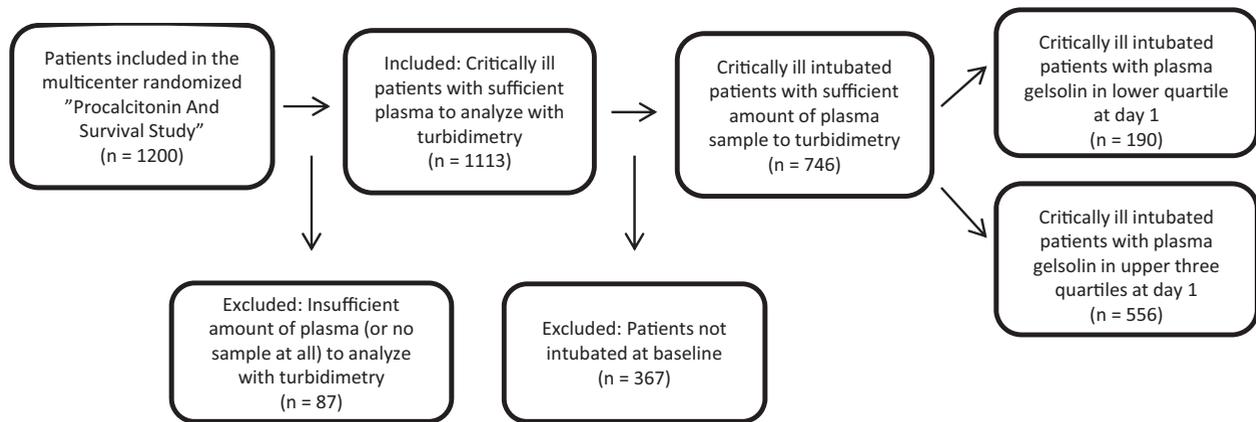
Fig. 1. **Flowchart of patients included.**

0.58–0.88, $P = 0.002$) (Table 2). Apart from gelsolin concentration below the 25th percentile, the chance of successful weaning within 28 days was decreased by severe sepsis/septic shock, PCT baseline level >1 μg/L, SPD baseline levels $>$85th percentile, and Apache II score ≥ 25, significantly (Table 2).

Successful weaning within 28 days was seen in 124/190 (65.3%) of patients with baseline gelsolin in the lower quartile. In the 3 upper quartiles, 404/556 (72.7%) of the patients were successfully weaned (Log-rank $P < 0.0001$). Seventeen patients in each group (Q1 vs. Q2–Q4) were still in requirement of mechanical ventilation at day 28. The remaining patients were successfully weaned or had died within the follow-up period.

We tested for interaction between surgical origin and baseline gelsolin level below the 25th percentile, because we found it plausible, that surgical patients had a different usage of gelsolin or had received more blood transfusions than the medical patients. The interaction between surgical origin and gelsolin in the lower quartile was not significant, however, a

trend was evident ($P = 0.08$). Based on this, we analyzed the surgical and medical patients separately. In the medical patients, baseline gelsolin level below the 25th percentile independently predicted a 40% reduction in chance of being successfully weaned within 28 days (HR 0.60, 95% CI 0.46–0.79, $P = 0.0002$). Conversely, in the surgical patients, the baseline gelsolin level did not affect the chance of being successfully weaned (HR 0.94, 95% CI 0.65–1.36, $P = 0.73$).

Patients with a baseline gelsolin below the 25th percentile had 10.9 ventilator-free days within 28 days, whereas the patients with a baseline gelsolin above the 25th percentile had 13.5 ventilator-free days within 28 days ($P = 0.006$).

Figure 2A illustrates the independence between gelsolin and SPD in predicting successful weaning in the medical patients.

Mortality related to the baseline gelsolin levels

Twenty-eight days mortality was not predicted by baseline gelsolin levels in the lower quartile (Table 3). Higher 28 days

TABLE 1. **Baseline characteristics of patients with baseline gelsolin level below the 25th percentile and the patients above the 25th percentile**

Characteristic	Gelsolin lower quartile (n = 190)	Gelsolin upper quartiles 2–4 (n = 556)	P values for differences
Age (year, median, IQR)	64 (56–73)	69 (59–76)	0.001
Gender (n male/n female)	103 (54.2)/87 (45.8)	300 (54.0)/256 (46.0)	1.0
Apache II score (median, IQR)	21 (16–27)	20 (14–26)	0.3
BMI (kg/m², median, IQR)	24.8 (22.0–27.8)	24.7 (22.2–27.7)	0.5
COPD n (%)	25 (13.2)	122 (21.9)	0.009
Severe sepsis/septic shock n (%)	116 (61.1)	184 (33.1)	<0.0001
Surgical origin n (%)	71 (37.4)	141 (25.4)	0.002
Acute thrombosis[*] n (%)	4 (2.1)	29 (5.2)	0.07
Chronic inflammatory disease[†] n (%)	14 (7.37)	29 (5.2)	0.3
Procalcitonin (μg/L, median, IQR)	12.3 (2.8–38.2)	2.61 (0.5–14.3)	0.0002
PaO₂/FiO₂ ratio kPa/mmHg (median, IQR)	21.0 (13.4–29.3)/157.5 (100.5–219.8)	19.6 (12.2–29.0)/147.0 (91.5–217.5)	0.8
SPD (ng/mL, median, IQR)	94.2 (55.6–172.7)	135.3 (78.9–314.2)	0.0002
ARDS n (%)	10 (3.6)	20 (5.3)	0.3
Gelsolin (mg/L, median, IQR)	29.1 (17.2–42.2)	90.0 (69.9–115.6)	<0.0001

[*]Acute myocardial infarction, pulmonary embolism, cerebral infarction, mesenteric embolism, and medulla spinalis infarction.
[†]Rheumatoid arthritis, Sjögren syndrome, fibromyalgia, spondylosis, hepatic cirrhosis, systemic lupus erythematosus, vasculitis, and chronic glomerulonephritis.
ARDS indicates acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SPD, surfactant protein D.

Table 2. **Predictors of successful weaning from mechanical ventilation within 28 days – Cox regression**

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (per year increase)	1.00	0.99–1.00	0.08	1.00	0.99–1.00	0.1
Gender (male/female)	1.03	0.87–1.22	0.7	0.98	0.82–1.17	0.8
Severe sepsis/shock (vs. milder or no infection)	**0.62**	**0.52–0.75**	**<10^{-4}**	**0.76**	**0.62–0.93**	**0.007**
Surgical origin (yes/no)	1.07	0.89–1.28	0.5	1.03	0.85–1.25	0.8
Acute thrombosis* (yes/no)	1.40	0.94–2.09	0.1	1.24	0.82–1.87	0.3
Chronic inflammatory disease† (yes/no)	0.78	0.52–1.15	0.2	0.87	0.58–1.30	0.5
PCT (≥1 μg/L vs. PCT <1 μg/L)	**0.61**	**0.50–0.73**	**<10^{-4}**	**0.71**	**0.58–0.88**	**0.002**
PaO$_2$/FiO$_2$ Q1 (vs. Q2–Q4)	**0.77**	**0.64–0.93**	**0.007**	0.84	0.69–1.02	0.08
SPD (≥85th percentile vs. SPD <85th percentile)	**0.79**	**0.64–0.96**	**0.02**	**0.74**	**0.60–0.92**	**0.006**
COPD (yes/no)	0.96	0.77–1.20	0.7	0.84	0.67–1.06	0.2
Apache II score (<25 vs. ≥25)	**0.70**	**0.58–0.85**	**0.0004**	**0.81**	**0.66–1.00**	**0.05**
Gelsolin Q1 (vs. Q2–Q4)	**0.67**	**0.55–0.82**	**10^{-4}**	**0.71**	**0.58–0.88**	**0.002**

Significant results (P < 0.05) are marked with **bold font**.
*Acute myocardial infarction, pulmonary embolism, cerebral infarction, mesenteric embolism, and medulla spinalis infarction.
†Rheumatoid arthritis, Sjögren syndrome, fibromyalgia, spondylosis, hepatic cirrhosis, systemic lupus erythematosus, vasculitis and chronic glomerulonephritis.
COPD indicates chronic obstructive pulmonary disease; PCT, procalcitonin; Q1, lower quartile; Q2–Q4, upper 3 quartiles; SPD, surfactant protein D.
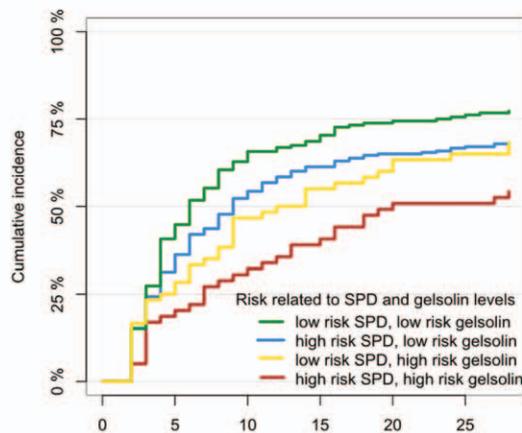
mortality was predicted by SPD baseline levels >85th percentile, COPD, Apache II score ≥25, chronic inflammatory disease, male gender, and increasing age (Table 3). Because of an interaction between surgical origin and baseline gelsolin below the 25th percentile in the analysis of successful weaning within 28 days, we tested the same interaction in the analysis of 28 days mortality. There was no interaction (P = 0.52).

Among the patients with baseline gelsolin below the 25th percentile, 66/190 (34.7%) died within the first 28 days. In the 3 upper quartiles 207/556 (37.2%) of the patients died within the first 28 days (Log-rank P = 0.56) (Fig. 3).

Alive and out of intensive care at day 14

The chance of being "alive and out of intensive care at day 14" was 31% lower for the patients with a baseline gelsolin level below the 25th percentile compared to the patients with baseline gelsolin levels above the 25th percentile (HR 0.69, 95% CI 0.54–0.89, P = 0.005) (Table 4). Besides gelsolin levels below the 25th percentile, lower chance of discharge from ICU within 14 days after admission was independently predicted by severe sepsis/septic shock, baseline PCT level >1 μg/L, SPD baseline levels >85th percentile, and Apache II score ≥25 (Table 4). Because of an interaction between
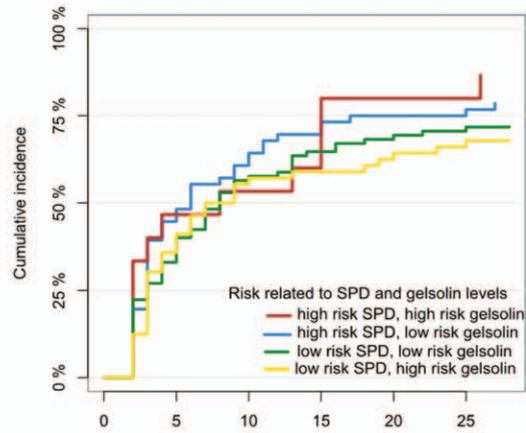
Fig. 2. **Successful weaning for medical and surgical patients.** A, Cumulative incidence curves showing successful extubation for patients with medical origin until day 28 for patients divided into 4 curves according to gelsolin and SPD. B, Cumulative incidence curves showing successful extubation for patients with surgical origin until day 28 for patients divided into 4 plots according to gelsolin and SPD. Low-risk SPD is defined as below median SPD level and high-risk SPD is defined as above median SPD level.

TABLE 3. **Predictors of 28 days mortality – Cox regression**

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (per year increase)	**1.04**	**1.02–1.04**	**<10⁻⁴**	**1.03**	**1.02–1.04**	**<10⁻⁴**
Gender (male/female)	1.18	0.93–1.50	0.2	**1.30**	**1.01–1.66**	**0.05**
Severe sepsis/shock (vs. milder or no infection)	1.19	0.94–1.51	0.2	1.12	0.86–1.45	0.4
Surgical origin (yes/no)	**0.65**	**0.49–0.87**	**0.003**	0.75	0.56–1.03	0.07
Acute thrombosis* (yes/no)	1.56	0.96–2.55	0.08	1.58	0.96–2.60	0.07
Chronic inflammatory disease† (yes/no)	1.47	0.94–2.29	0.09	**1.64**	**1.04–2.60**	**0.03**
PCT >1 μg/L (vs. PCT <1 μg/L)	1.30	0.98–1.71	0.07	1.32	0.97–1.79	0.08
PaO₂/FiO₂ Q1 (vs. Q2–Q4)	1.13	0.88–1.44	0.4	0.97	0.75–1.26	0.8
SPD (≥85th percentile vs. SPD <85th percentile)	**1.73**	**1.35–2.21**	**<10⁻⁴**	**1.45**	**1.11–1.88**	**0.006**
COPD (yes/no)	**1.62**	**1.24–2.12**	**0.0005**	**1.57**	**1.18–2.09**	**0.002**
Apache II score (<25 vs. ≥25)	**1.67**	**1.31–2.13**	**<10⁻⁴**	**1.53**	**1.18–1.99**	**0.001**
Gelsolin Q1 (vs. Q2–Q4)	0.92	0.70–1.22	0.6	1.04	0.77–1.39	0.8

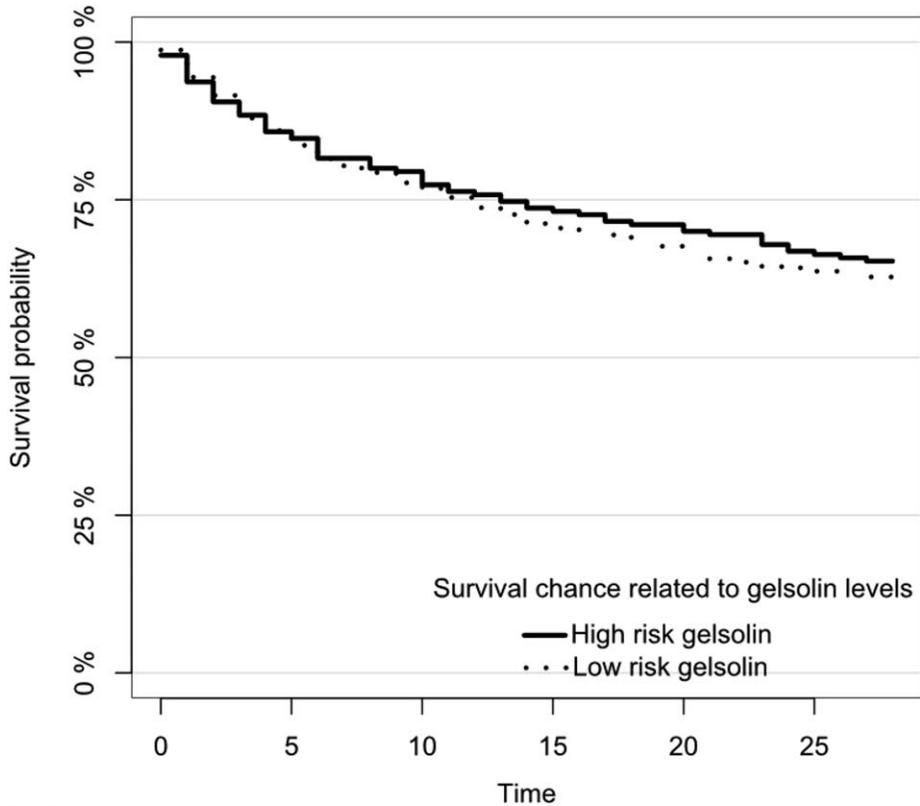Significant results (P < 0.05) are marked with **bold font**.
*Acute myocardial infarction, pulmonary embolism, cerebral infarction, mesenteric embolism, and medulla spinalis infarction.
†Rheumatoid arthritis, Sjögren syndrome, fibromyalgia, spondylosis, hepatic cirrhosis, systemic lupus erythematosus, vasculitis, and chronic glomerulonephritis.
COPD indicates chronic obstructive pulmonary disease; PCT, procalcitonin; Q1, lower quartile; Q2–Q4, upper 3 quartiles; SPD, surfactant protein D.

surgical origin and baseline gelsolin below the 25th percentile in the analysis of successful weaning within 28 days, we tested the same interaction in the analysis of "alive and out of intensive care at day 14." There was no interaction (P = 0.14).

Among patients with baseline gelsolin below the 25th percentile 83/190 (43.7%) were "alive and out of intensive care at day 14", whereas 307/556 (55.2%) of the patients with baseline gelsolin levels in upper 3 quartile were "alive and out of intensive care at day 14" (Log-rank P = 0.007).

FIG. 3. **Kaplan–Meier curve showing mortality.** Kaplan–Meier curve showing mortality for patients with baseline gelsolin levels below the 25th percentile and patients with baseline gelsolin above the 25th percentile. There was no interaction between surgical origin and baseline gelsolin level below the 25th percentile (P = 0.71).

TABLE 4. **Predictors of "alive and out of ICU at day 14" – Cox regression**

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (per year increase)	**0.99**	**0.99–1.00**	**0.037**	0.99	0.99–1.00	0.053
Gender (male vs. female)	1.032	0.85–1.26	0.75	1.01	0.83–1.24	0.90
Severe sepsis/septic shock (vs. milder or no infection)	**0.58**	**0.47–0.72**	**<10⁻⁴**	**0.72**	**0.57–0.91**	**0.006**
Surgical origin (yes vs. no)	1.050	0.85–1.30	0.66	1.03	0.82–1.30	0.79
Acute thrombosis* (yes vs. no)	1.24	0.75–2.047	0.40	1.13	0.68–1.89	0.63
Chronic inflammatory disease† (yes vs. no)	0.73	0.45–1.21	0.22	0.84	0.50–1.49	0.49
PCT >1 µg/L (vs. PCT <1 µg/L)	**0.56**	**0.45–0.69**	**<10⁻⁴**	**0.67**	**0.53–0.84**	**0.0008**
PaO$_2$/FiO$_2$ Q1 (vs. Q2–Q4)	**0.77**	**0.62–0.96**	**0.021**	0.87	0.69–1.09	0.22
SPD (≥85th percentile vs. SPD <85th percentile)	**0.77**	**0.61–0.98**	**0.032**	**0.73**	**0.56–0.94**	**0.014**
COPD (yes/no)	0.90	0.69–1.17	0.43	0.79	0.60–1.04	0.094
Apache II score (<25 vs. ≥25)	**0.64**	**0.51–0.81**	**0.0002**	**0.76**	**0.60–0.97**	**0.028**
Gelsolin Q1 (vs. Q2–Q4)	**0.63**	**0.50–0.81**	**0.0002**	**0.69**	**0.54–0.89**	**0.0045**

Significant results (P < 0.05) are marked with **bold font**.
*Acute myocardial infarction, pulmonary embolism, cerebral infarction, mesenteric embolism, and medulla spinalis infarction.
†Rheumatoid arthritis, Sjögren syndrome, fibromyalgia, spondylosis, hepatic cirrhosis, systemic lupus erythematosus, vasculitis, and chronic glomerulonephritis.
COPD indicates chronic obstructive pulmonary disease; PCT, procalcitonin; Q1, lower quartile; Q2–Q4, upper 3 quartiles; SPD, surfactant protein D.

Patients with a baseline gelsolin below the 25th percentile had 10.2 ICU-free days within 28 days, whereas the patients with a baseline gelsolin above the 25th percentile had 12.4 ICU-free days within 28 days (P = 0.018).

Endothelial damage is not associated with low gelsolin level

There was no correlation between baseline gelsolin levels and baseline soluble sTM, correlations coefficient −0.04 (95% CI −0.11 to 0.034, P = 0.29) or change of sTM from day 1 to 4, correlation coefficient -0.074 (95% CI −0.16 to 0.014, P = 0.10).

DISCUSSION

We observed that gelsolin is an independent marker of successful weaning from mechanical ventilation within 1 month in critically ill patients with ventilator-demanding acute respiratory failure and duration of ICU stay. However, gelsolin was not found to be a marker of mortality. This might indicate that gelsolin is not a marker of systemic illness per se, but rather of degree of long-lasting pulmonary injury. The values of measured gelsolin in this population were much lower than for healthy individuals. This was expected, because the patients were all severely ill at baseline. Furthermore, and surprisingly, we did not find a correlation between baseline gelsolin concentration and level or change in sTM, which indicates that the lung damage detected by the low gelsolin levels is not mediated by endothelial damage. Since SPD is a well-known and clinically used biomarker of lung damage at this point, the analysis of successful weaning within 28 days was adjusted for baseline SPD >85th percentile. We found that both markers (gelsolin and SPD) independently of each other and of the remaining covariates predicted the primary end point of successful weaning from ventilation at day 28. It has been shown in previous studies that a surgical trauma may lead to decreasing gelsolin levels (11). Thus, a low gelsolin may have highly differing causes among medical and surgical patients. Therefore, we

conducted an interaction analysis of the primary end point between surgical versus medical reasons for admission to the ICU and a low baseline gelsolin; P = 0.054. We thus also conducted separate analyses of the primary end point among medical and surgical patients. We observed that a low gelsolin strongly predicted persistent ventilator-demanding respiratory failure in medical critically ill patients, but it was not a predictor of this end point among surgical patients (Fig. 2).

In a study with 77 trauma patients, the duration of ventilator-demanding respiratory failure and duration of stay at ICU seemed increased among patients with lowered circulating gelsolin (>2 standard deviations under mean of healthy controls) (11). This is consistent with our results, where n = 746. However, earlier studies have also shown that a lower gelsolin level was associated with a higher mortality rate, which is not consistent with our findings (11, 10). Since our study is approximately 10 times larger than other studies of gelsolin in such patients, type I error in the previous and smaller studies seems to be a possible explanation for the discrepancy.

Apart front the actin-scavenging function, gelsolin can help in the defense against lung infections by activating phosphorylation of macrophage nitrogen oxide synthase type III (NOS3) (33). NOS3 is an enzyme with bactericidal function within the macrophages of the lungs. This indicates that gelsolin is as well a potential immune modulator for a stronger defense against primary and secondary bacterial pneumonia (33). This provides an alternative, or additional, positive characteristic of gelsolin in circulation.

Apart from the value of gelsolin as a biomarker of persistent respiratory failure, it may have therapeutic implications. In a murine study, gelsolin infusion was observed to reduce inflammation-induced lung damage after burn traumas (34). There has also been observed a significantly lowered morbidity after surgery on septic rats receiving gelsolin infusion compared to septic rats after surgery not receiving gelsolin infusion (35).

As a future perspective, first, our result can help stratifying patients with acute respiratory failure in risk of long-term mechanical ventilation. Second, our results represent the largest

clinical material to explore this biomarker in a context of critically ill and its possible role in lung protection. Trials could use gelsolin as a way to optimize power, since patients with low gelsolin are those in highest risk of severe prolonged lung damage.

Strengths and limitations of the study

The statistical analysis was made with multiple Cox regression adjusted for known and suspected gelsolin-consuming conditions, e.g., comorbidities. There is limited knowledge about which conditions cause consumption of gelsolin. This is a limitation in the statistical analysis. The surgical patients may have actin release because of a surgical procedure, whereas intubated medical patients may have actin release because of lung damage. Besides, the different pattern in actin release between the surgical and medical patients, there could be a part of the surgical patients who have received blood transfusions, which could change both the actin and gelsolin levels. The reasons for this interaction need to be further investigated in the future. A minor limitation is that plasma gelsolin was only measured once in every sample and not as a duplicate. The decision to extubate a patient was done in conference between at least 2 ICU specialists according to the current guidelines (36), however, written criteria in the protocol were not provided. This is a potential limitation, however, gelsolin laboratory analysis was performed later than extubation, thus bias would not be likely. Tests on spontaneous breathing and awakening are not reported as well as data on sedation.

The strengths of this study are the large sample size and the detailed registration of many variates to every patient up to day 28 which allowed us to adjust for important confounding factors of the association between gelsolin and the investigated outcomes. Data were collected in accordance with good clinical practice as it was pursued to ensure a good quality of data.

CONCLUSION

Actin-scavenger gelsolin is an independent and strong predictor of persisting ventilator-demanding respiratory failure in medical intensive care patients. However, it is not associated with mortality. We show that both gelsolin and SPD carry separate prognostic properties and that combining these 2 biomarkers increases the prediction of persistent respiratory failure in critically ill patients. Our findings indicate that gelsolin may play a separate protective role in acute lung damage. As a future perspective, our findings may have important implications for risk stratification and for early guidance of therapeutic interventions directed toward minimizing lung injury.

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