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Short title: High-flow nasal oxygen therapy in severe COVID-19

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WHAT'S NEW?

The clinical presentation of coronavirus disease 2019 (COVID-19) varies in severity from asymptomatic infection to severe illness. A significant proportion of patients present with a rapidly progressing acute respiratory failure and require invasive mechanical ventilation. High-flow nasal oxygen therapy (HFNO) is a technique to deliver heated and humidified oxygen at high flows through a nasal cannula. The HFNO therapy in acute hypoxemic respiratory failure may help avoid intubation and mechanical ventilation. This prospective observational study showed that nearly half of patients with severe COVID-19 pneumonia eventually require invasive mechanical ventilation and almost third of these patients die within 30 days from hospital admission. Our results suggest that the ROX index (defined as the ratio of SpO2/FiO2 to respiratory rate) may be a useful tool for stratification of HFNO failure risk in this population.
ABSTRACT

**Introduction:** A significant proportion of patients with COVID-19 present with a rapidly progressing severe acute respiratory failure (ARF).

**Objectives:** We aimed to assess the therapeutic success of high-flow nasal oxygen (HFNO) in severe ARF in the course of COVID-19 in a noncritical care setting as well as to identify predictors of HFNO failure.

**Patients and methods:** This prospective observational study was conducted between March and December 2020. We enrolled all consecutive hospitalized patients with confirmed SARS-CoV-2 infection in whom HFNO therapy was used. The primary outcome measure was death or endotracheal intubation within 30 days from admission.

**Results:** Of the 380 patients with COVID-19, 116 individuals (30.5%) requiring HFNO due to severe pneumonia were analyzed. The primary outcome, defined as death or endotracheal intubation within 30 days from admission, occurred in 54 patients (46.6%). The overall 30-day mortality was 30.2% (35/116) in the entire cohort and 64.7% (34/51) among patients requiring endotracheal intubation. A multivariable analysis revealed that the ROX index measured within the first 12 hours of therapy below 3.85 was related to increased mortality (hazard ratio, 5.86; 95% CI, 3.03–11.35) compared with the ROX index of 4.88 or higher.

**Conclusions:** This study suggests that nearly half of patients treated with HFNO due to severe COVID-19 pneumonia will require mechanical ventilation. The ROX index is a useful tool for predicting HFNO failure in this population.
INTRODUCTION

The clinical presentation of coronavirus disease 2019 (COVID-19) is highly variable and affects multiple organs, with predominant involvement of the respiratory system. Approximately 15% of cases are severe, warranting hospitalization, and 5% of patients require admission to the intensive care unit (ICU).[1] The highly contagious nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in conjunction with the lack of effective causal treatment led to an exponential increase in the number of cases and a huge burden on healthcare systems globally. Since the first Polish case of COVID-19 was confirmed in March 2020, almost 1.3 million Polish citizens got infected with SARS-CoV-2, with a peak monthly incidence of 400,000 new active cases in November. Poland is characterized by one of the lowest ICU-to-hospital bed ratios in the European Union (2%–5%), rendering the public healthcare system particularly prone to failure in the face of increased patient load.[2,3]

A significant proportion of patients present with a rapidly progressing acute respiratory failure (ARF) and eventually require mechanical ventilation. The initially suggested approach included early intubation and mechanical ventilation with lung-protective strategy recommended by the ARDS Network trial.[4] Since the mortality of invasively ventilated patients remained high, it was hypothesized that some patients with severe COVID-19 pneumonia may benefit from other oxygenation improvement strategies allowing to avoid invasive mechanical ventilation and its adverse effects, that is, ventilator-induced lung injury and ventilator-associated pneumonia.[5,6] Hence, high-flow nasal oxygen (HFNO) therapy was suggested as an optimal treatment modality in this setting.

The HFNO therapy involves delivery of oxygenated gas, heated and humidified to body conditions, via a nasal cannula at a maximum flow up to 80 l/min.[7,8] The therapy is believed to have numerous benefits, including adequate humidification, reduction of
anatomical dead space and work of breathing, as well as an increase in end-expiratory lung volume thanks to the provision of positive end-expiratory pressure. During the past years, its use has extended in the critical care setting to the treatment of hypoxemic ARF after extubation and in the postoperative period in high-risk or obese patients.[9] Previous studies, mainly retrospective and with a limited sample size, suggested potential benefit associated with the use of HFNO in the treatment of respiratory failure in COVID-19.[10–13]

Facing the growing number of patients with severe respiratory failure due to COVID-19 with the insufficient ICU resources, our tertiary center adopted the use of HFNO by experienced respiratory physicians in noncritical care setting. The aim of this study was to assess the therapeutic success of HFNO in severe respiratory failure in the course of COVID-19. Our secondary goal was to identify factors associated with HFNO failure.

PATIENTS AND METHODS

Study design

This was a prospective observational study conducted between March and December 2020 in the Department of Pulmonology and Allergology, University Hospital in Kraków, Poland. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Jagiellonian University Medical College, Kraków, Poland (KBET 1072.6120.145.2020, Chairperson Prof. Piotr Thor) on May 28, 2020. The study subjects gave written informed consent and were informed that the HFNO was introduced regardless of this study, following guidelines for the treatment of respiratory failure in COVID-19.

Patients and data collection

We enrolled all consecutive patients with confirmed SARS-CoV-2 infection admitted to the hospital in whom HFNO therapy was used. We excluded patients in whom the goal of
care did not include intubation and invasive mechanical ventilation and those in whom HFNO was used after successful extubation. Study personnel collected detailed demographic and clinical data (including symptoms, comorbidities, vital signs, laboratory results, and imaging studies) based on the interviews with patients or their relatives and available medical records.

**High-flow oxygen therapy**

The indication for HFNO administration was a severe respiratory failure defined as requirement to receive oxygen supplementation with $\text{FiO}_2$ of 50% or higher to achieve satisfactory oxygen saturation ($\text{SpO}_2$). High-flow nasal oxygen was delivered by Airvo 2 device (Fisher&Paykel healthcare, Irvine, California, United States). The HFNO flow and fraction of inspired oxygen ($\text{FiO}_2$) were titrated to achieve an oxygen saturation ($\text{SpO}_2$) between 92% and 96% for patients without hypercapnia and between 88% and 92% for those with hypercapnia. In each patient, we recorded initial and maximal HFNO settings. Additionally, within the first 12 hours of HFNO therapy, we recorded $\text{FiO}_2$, $\text{SpO}_2$, and respiratory rate to calculate the ROX index. Respiratory rate and $\text{SpO}_2$ were measured automatically by continuous patient monitoring systems. According to a formula presented by Roca et al.[14] ROX index is defined as the ratio of $\text{SpO}_2$/FiO$_2$ to respiratory rate. For subjects in whom invasive mechanical ventilation was initiated within 12 hours from admission, we recorded the above parameters at the time of the decision on intubation.

**Outcomes**

The primary outcome was a composite of death and endotracheal intubation within 30 days from enrollment.

**Statistical analysis**
Categorical variables were presented as numbers (percentages), whereas continuous variables were reported as medians (interquartile range) or means (standard deviation) depending on variable distribution. Quantitative data were analyzed using the t test or Mann–Whitney test. An adjusted analysis of factors associated with the incidence of primary outcome was performed using a Cox proportional hazard model including selected variables, such as age, sex, diagnosis of obesity, D-dimer level on admission, disease stage (defined as early for patients with ≤7 days from symptoms onset to HFNOT initiation, and as late for patients with >7 days from symptoms onset to HFNOT initiation), and ROX category (≥4.88, 3.85–4.87, and <3.85).[14] The analysis was performed after confirmation that the proportional hazards assumption was justified. The variables included in the model were selected based on our knowledge as well as the available evidence. This was a complete-case analysis. A 2-sided P value of less than 0.05 was considered significant. All analyses were performed using R version 3.6.0 (R Project) with the following packages: rms, survival, survminer and ggplot2.

RESULTS

Patients

The study group initially comprised 380 patients with confirmed COVID-19, of whom 125 (32.9%) required HFNO. Of those, 9 patients (7.2%) in whom endotracheal intubation was not the goal of care were excluded. Thus, 116 patients were included in the final analysis (Figure 1). No patients were lost to 30-day follow-up.

The study group included 91 men (78.4%) and 25 women (21.6%). The median age was 61 years (IQR, 51–70). The most common comorbidities were hypertension (57.8%), obesity (37.1%), and diabetes (31%). On admission, the median Modified Early Warning Score (MEWS) and the SpO₂/FiO₂ ratio were 2 (IQR, 1–3) and 101.1 (IQR, 94.7–192.3),
respectively. Dexamethasone was administered in 104 patients (89.7%); remdesivir, in 71 (61.2%); and convalescent plasma, in 17 patients (14.7%). Detailed demographic and clinical characteristics of the study group are presented in Table 1.

**High-flow oxygen therapy**

Among the 116 patients requiring HFNO, the median initial flow and FiO$_2$ were 60 (IQR, 50–60) and 80 (IQR, 65–90), while the median maximum values were 60 (IQR, 60–60) and 92 (IQR, 77.5–95), respectively. The ROX index (n = 113) calculated within the first 12 hours of HFNO therapy was 4.88 or higher in 63 patients (55.8%), 3.85 to less than 4.88 in 30 patients (26.5%), and less than 3.85 in 20 patients (17.7%). More detailed data concerning HFNO and arterial blood gas analysis are presented in Table 1. The median hospitalization time was 20 days (IQR, 13–29), while the median ICU stay was 10 days (IQR, 6–15.5).

**Primary outcome**

The primary outcome occurred in 54 patients (46.6%). The Kaplan-Meier curve showing the probability of not developing the primary outcome stratified by the ROX index category is presented in Figure 2. Endotracheal intubation was performed in 51 patients (44%), while the 30-day mortality rate was 30.2% (35 of 116 patients). The 30-day mortality rate among patients requiring endotracheal intubation was 64.7% (34 of 51 patients).

The univariable analysis showed that patients in whom the primary outcome occurred were older (63 vs 58 years, $P=0.01$), had higher baseline lactate dehydrogenase levels (555 vs 504.5 U/l, $P=0.01$), higher lactate levels (1.6 vs 1.3, $P=0.03$), and had a significantly lower ROX index (4.49 vs 5.47, $P<0.001$) compared with the remaining study group (Table 2). We did not find any differences in the duration of hospitalization (18 vs 20 days, $P=0.60$). There was also no difference in the median time from HFNO therapy initiation to endotracheal
intubation between survivors and nonsurvivors (1 vs 3 days, \(P=0.45\)). The groups did not differ in terms of systemic steroid (93.5 vs 85.2%, \(P=0.24\)), remdesivir (67.7 vs 53.7%, \(P=0.18\)), and convalescent plasma administration (16.1 vs 13%, \(P=0.83\)).

The multivariable analysis revealed that after adjustment for age, sex, obesity, and baseline D-dimer levels, disease stage, the ROX index between 3.85 and 4.88 was not associated with increased mortality (hazard ratio [HR], 1.46; 95% CI, 0.73–2.93), while the ROX index below 3.85 was related to increased mortality (HR, 6.1; 95% CI, 3.04–12.26) compared with a ROX index of 4.88 or higher (set as a reference value). The results of multivariable analysis are summarized in Figure 3 and Table 3.

**DISCUSSION**

This single-center prospective observational study revealed that nearly half of patients with severe COVID-19 pneumonia eventually require invasive mechanical ventilation and almost third of these patients die within 30 days from admission to the hospital. Moreover, our results suggest that the ROX index is a valuable tool for stratification of HFNO failure risk in this population. To our knowledge, this is the first study of HFNO in severe COVID-19 in Europe that was conducted on a cohort including more than 100 patients.

High-flow nasal oxygen therapy is more than just oxygen supplementation. It constitutes a very well-tolerated and easy-to-apply ventilatory assist device. It is widely accepted in the treatment of hypoxemic respiratory failure and its use is recommended by the Surviving Sepsis Campaign over conventional oxygen therapy in patients with severe COVID-19 with ARF.[15,16] A meta-analysis of 9 randomized controlled trials of acute hypoxemic respiratory failure in non-COVID patients requiring HFNO revealed lower intubation rates without any influence on survival. Over half of our patients with baseline high risk for endotracheal intubation eventually avoided the primary outcome, which suggests
that HFNO could potentially facilitate the prevention of mechanical ventilation in the COVID-19 population. However, any final conclusions in this respect are hindered by the lack of a control group. Therefore, randomized controlled trials concerning the efficacy of HFNO in the prevention of intubation among patients with severe COVID-19 pneumonia are warranted and highly anticipated.

Relatively high intubation and mortality rates observed in our cohort are consistent with the remaining available studies.[17–19] Another key clinical aspect concerning the treatment of ARF in the course of COVID-19 is the optimal timing of intubation. It has been well proven that delay of intubation in severe ARF is associated with worse outcomes.[20] A similar association in the COVID-19 population remains unclear. In our study, there was no difference between survivors and nonsurvivors in time from admission to endotracheal intubation. Two multicenter studies revealed contradictory results. A study by Hyman et al. showed that each additional day between hospital admission and intubation is associated with an increased in-hospital mortality among patients with severe ARF in the course of COVID-19, while Dupuis and colleagues revealed that early intubation of patients admitted to ICU due to severe COVID-19 resulted in increased mortality and number of ICU-acquired infections. [21,22]

The most important practical aim of this study was to evaluate potential factors enabling identification of patients at greater risk of HFNO failure early in the course of the treatment. The ROX index is considered a useful clinical tool in the prediction of HFNO success defined as avoiding endotracheal intubation among patients with acute hypoxemic respiratory failure.[23] It was validated in a multicenter prospective study on patients with non-COVID pneumonia and hypoxemic respiratory failure. The value of 2.85 or lower after 2 hours, 3.47 or lower after 6 hours, and 3.85 or lower after 12 hours of treatment were predictors of HFNO failure with a specificity of 98% to 99%. Our study suggests that the
ROX index is a valuable predictive score among patients with severe COVID-19 pneumonia. We have found that the ROX index values lower than 3.85 measured in the first 12 hours after HFNO initiation, as proposed by Roca et al [18], was associated with a higher rate of intubation and death.

Relatively high intubation and mortality rates observed in our cohort are consistent with the remaining available studies. Compared with a study by Calligaro et al [10], the proportion of patients that required endotracheal intubation was somewhat lower. Additionally, the 30-day mortality rate in our cohort was 30% and all survivors were discharged from the hospital at the time of data analysis, while in the latter study, the in-hospital mortality rate was 46%. Another important observation is a very high mortality rate among patients requiring mechanical ventilation after HFNO failure in both studies (64% in our study as compared with 76% in the study by Calligaro et al [10]). Better clinical outcomes observed in our study might be partially explained by a lower severity of ARF in our sample reflected by lower ROX index values in patients who developed primary outcome (4.49 vs 2.41) as compared with those who did not (5.47 and 3.26). In a similar retrospective study, although involving a smaller cohort (n = 62), the authors observed a similar median ROX index accounting to 5.4. Zucman et al [12] reported the need to use invasive mechanical ventilation in 63% of the population; however, interestingly, the overall mortality in the ICU was markedly lower and amounted to 17%.

The strength of this study was its prospective design and a relatively large sample collected over a short period of time, with 30-day follow-up completed in all participants. Patients with severe COVID-19 without contraindications received treatment including systemic steroids, LMWH, and remdesivir according to current recommendations; thus, differences in pharmacotherapy were less possible to influence outcomes. It is the first report on HFNO therapy provided by non-ICU personnel in a larger cohort.
We are aware of the limitations of this study. The lack of randomization and a control group significantly increases the risk of bias in this study. The decision on intubation was not protocolized but was made by an experienced anesthesiologist and pulmonologist according to Polish guidelines, based on the SpO₂/FiO₂ index, respiratory distress signs, age, and comorbidity status.[24] A possible bias in the assessment of ROX as a predictor of primary outcome is the fact that even though it was not formally calculated, its components such as SpO₂, FiO₂, and respiratory rate were factors that were taken into account by the physician in making the decision about intubation.

**CONCLUSIONS**

In conclusion, our study suggests that HFNO could potentially be a valuable modality in the treatment of severe hypoxemic ARF in the course of COVID-19 in a noncritical care environment. More than half of this cohort did not reach the primary outcome defined as intubation and mechanical ventilation or death and were successfully weaned from HFNO. Yet, it must be emphasized that prognosis for patients who fail on HFNO and finally are mechanically ventilated is poor. Finally, the ROX index was shown to be a useful tool in predicting patients at high risk of HFNO failure.

**Contribution statement:** NCW and KS conceived the idea for the study. KP, KG, and TS contributed to the design of the research. NCW, KP, KG, TS, AK, PN, and JK were involved in data acquisition. KP, SL, and KW analyzed the data. All authors edited and approved the final version of the manuscript.
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Table 1. Baseline characteristics of the study group.

| Parameter                                              | Value                                      |
|-------------------------------------------------------|--------------------------------------------|
| **Demographic data, measurements, and comorbidities**  |                                            |
| Age (years)                                           | 61 (51–70)                                 |
| Sex, male, n (%)                                      | 91 (78.4)                                  |
| BMI (kg/m²)                                            | 29.41 (26.08–32.95)                       |
| MEWS score on admission                               | 2 (1–3)                                    |
| Hypertension, n (%)                                   | 67 (57.8)                                  |
| Chronic heart failure, n (%)                          | 14 (12.1)                                  |
| Coronary artery disease, n (%)                        | 17 (14.7)                                  |
| Diabetes mellitus, n (%)                              | 36 (31.0)                                  |
| Obesity, n (%)                                        | 43 (37.1)                                  |
| Chronic kidney disease, n (%)                         | 12 (10.3)                                  |
| Obstructive lung disease, n (%)                       | 13 (11.2)                                  |
| **Laboratory results on admission**                   |                                            |
| D-dimer (mg/l)                                        | 1.17 (0.78–3.29)                           |
| LDH (U/l)                                             | 522 (392–620,50)                           |
| CRP (mg/l)                                            | 125.50 (72.40–199.25)                     |
| IL-6 (pg/ml)                                          | 69.19 (30.52–110.33)                      |
| Arterial blood gases                                  |                                            |
| pO₂ (mmHg)                                            | 65 (56.50–77.55)                           |
| pCO₂ (mmHg)                                           | 34 (31.10–38.15)                           |
| pH (mmHg)                                             | 7.45 (7.42–7.48)                           |
| Lactate (mmol/l)                                      | 1.40 (1.20–1.90)                           |
Data are presented as median (interquartile range) unless otherwise indicated.

* patients receiving LMWH

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HFNO, high flow nasal oxygen; IL-6, interleukin 6; LDH, lactate dehydrogenase; LMWH, low-molecular-weight heparin; MEWS, Modified Early Warning Score; SpO\textsubscript{2}/FiO\textsubscript{2}, ratio of blood oxygen saturation to inspired oxygen fraction.

| Oxygen requirement and respiratory parameters |  |
|-----------------------------------------------|------------------|
| SpO\textsubscript{2}/FiO\textsubscript{2} on admission | 101.05 (94.74–192.25) |
| Initial FiO\textsubscript{2} on HFNO | 80 (65–90) |
| Initial respiratory rate on HFNO | 22 (20–28) |
| Max FiO\textsubscript{2} on HFNO | 92 (77.5–95) |
| Initial flow on HFNO | 60 (50–60) |
| Max flow on HFNO | 60 (60–60) |
| No. of days with HFNO | 6 (2–9) |
| ROX index at 12 h | 5.11 (4.11–6.69) |

| Pharmacotherapy |  |
|-----------------|------------------|
| Systemic steroids, n (%) | 104 (89.7) |
| Remdesivir, n (%) | 71 (61.2) |
| Convalescent plasma, n (%) | 17 (14.7) |
| LMWH, n (%)* |  |
| Therapeutic dose | 68 (58.6) |
| Intermediate dose | 41 (35.3) |
| Prophylactic dose | 5 (4.3) |
| Parameter                              | Primary outcome not achieved | Primary outcome achieved |
|---------------------------------------|-----------------------------|-------------------------|
|                                       | N = 62                      | N = 54                  |
|                                       |                             | P value                 |
| **Demographic data, measurements, and comorbidities** |                             |                         |
| Age, years                            | 58 (45–66)                  | 63 (57.25–72.75)        | 0.01                     |
| Sex, male, n (%)                      | 11 (17.7)                   | 14 (25.9)               | 0.40                     |
| BMI, kg/m²                             | 28.73 (25.72–32.65)         | 30.42 (27.22–33.06)     | 0.23                     |
| MEWS score on admission,              | 2 (1–2)                     | 2 (1–3)                 | 0.01                     |
| Hypertension, n (%)                   | 37 (59.7)                   | 30 (55.6)               | 0.80                     |
| Chronic heart failure, n (%)          | 9 (14.5)                    | 5 (9.3)                 | 0.56                     |
| Coronary artery disease, n (%)        | 6 (9.7)                     | 11 (20.4)               | 0.17                     |
| Diabetes mellitus, n (%)              | 17 (27.4)                   | 19 (35.2)               | 0.48                     |
| Obesity, n (%)                        | 21 (33.9)                   | 22 (40.7)               | 0.57                     |
| Chronic kidney disease, n (%)         | 4 (6.5)                     | 8 (14.8)                | 0.24                     |
| Obstructive lung disease, n (%)       | 7 (11.3)                    | 7 (13)                  | 0.78                     |
| **Laboratory results on admission**   |                             |                         |
| Dimer D, mg/l                         | 1.11 (0.66–3.85)            | 1.43 (0.91–2.72)        | 0.16                     |
| LDH, U/l                              | 504.50 (370.75–567.50)      | 555 (424–815)           | 0.01                     |
| CRP, mg/l                             | 120.50 (74.28–184.25)       | 143.50 (67.53–211.25)   | 0.48                     |
| IL-6, pg/ml                           | 51.79 (25.12–108)           | 80.55 (45.81–117.75)    | 0.09                     |
| Arterial blood gases            | pO₂, mmHg       | pCO₂, mmHg      | pH               | Lactate, mmol/l |
|--------------------------------|-----------------|-----------------|------------------|----------------|
|                                | 70.20 (59.10–81.75) | 34.30 (30.90–38.58) | 7.46 (7.43–7.49) | 1.30 (1.02–1.60) |
|                                | 63 (54–70)      | 33.60 (31.20–38) | 7.44 (7.42–7.47) | 1.60 (1.28–2.02) |
|                                | 0.005           | 0.70            | 0.16             | 0.03            |

| Oxygen requirement and respiratory parameters |
|-----------------------------------------------|
| SpO₂/FiO₂ on admission, median (IQR)          | 103.89 (100–214.77) | 98.89 (89.47–161.67) |
| Initial FiO₂ on HFNO                          | 75 (60–85)         | 86 (70–93)          |
| Initial respiratory rate on HFNO              | 22 (20–26)         | 24 (20–28)          |
| Max FiO₂ on HFNO                              | 85 (70–92)         | 95 (93–95)          |
| Initial flow on HFNO                          | 60 (50–60)         | 60 (60–60)          |
| Max flow on HFNO                              | 60 (50–60)         | 60 (60–60)          |
| No. of days with HFNO                         | 7 (5.25–10.75)     | 2 (2–5.75)          |
| ROX index at 12 h                             | 5.47 (4.64–7.13)   | 4.49 (3.63–5.91)    |
| Pharmacotherapy                               |                   |                   |
| Systemic steroids, n (%)                      | 58 (93.5)         | 46 (85.2)          |
| Remdesivir, n (%)                             | 42 (67.7)         | 29 (53.7)          |
| Convalescent plasma, n (%)                    | 10 (16.1)         | 7 (13.0)           |
| LMWH, n (%)                                   |                   |                   |
| Therapeutic dose                              | 32 (52.5)         | 36 (67.9)          |
| Intermediate dose                             | 28 (45.9)         | 13 (24.5)          |
| Prophylactic dose                             | 1 (1.6)           | 4 (7.5)            |

Data are presented as median (interquartile range) unless otherwise indicated.

Abbreviations: see Table 1
| Variable          | HR  | 95% CI        |
|-------------------|-----|---------------|
| ROX Index         |     |               |
| ≥ 4.88            | Ref.| Ref.          |
| 3.85 to <4.88     | 1.46| 0.73 - 2.93   |
| <3.85             | 6.10| 3.04 - 12.26  |
| Age, years        | 1.02| 0.99 - 1.04   |
| Male sex          | 1.07| 0.55 - 2.11   |
| Obesity           | 1.14| 0.65 - 2.01   |
| Dimer D, mg/l     | 1.00| 0.98 - 1.01   |
| Late disease stage| 0.75| 0.42 -1.35    |
Figure 1. Study flow-chart.
Figure 2. Forrest plot summarizing the results of multivariable analysis.

Figure 3. Kaplan-Meier curves showing 30-day incidence of primary outcome stratified by the ROX index category.