Diagnostic, prognostic and therapeutic strategies in critically ill COVID–19 patients

Valk, C.M.A.

Publication date
2022

CHAPTER 10

Summary of the Thesis

This thesis is a collection of investigations focusing on classification and prognostication, and strategies to improve oxygenation in patients with acute hypoxemic respiratory failure due to coronavirus diseases 2019 (COVID–19).

The overarching aims of this thesis were:

1. To determine how acute respiratory distress syndrome (ARDS) can be diagnosed in patients with acute hypoxemic respiratory failure due to COVID–19 that do not receive ventilatory support with a minimum of 5 cm H_2O positive end–expiratory pressure (PEEP);
2. To study the prognostic performance of the 'Radiographic Assessment of Lung Edema' (RALE) score of the chest X–ray (CXR) and the 'computer tomography (CT) severity score' in patients with ARDS due to COVID–19;
3. To investigate the association of early PEEP settings with outcome in patients with ARDS due to COVID–19;
4. To investigate the association of early prone positioning with outcome in patients with ARDS due to COVID–19; and
5. To investigate the association of awake prone positioning with outcome in non–intubated patients with acute hypoxemic respiratory failure due to COVID–19.

The overarching hypothesis of this thesis were:

1. That ARDS can be diagnosed in patients with acute hypoxemic respiratory failure due to COVID–19 that do not receive ventilatory support with a 5 cm H_2O PEEP;
2. That the RALE score has prognostic capacity in patients with ARDS due to COVID–19, and that the prognostic capacity is comparable to that of the CT severity score;
3. That early PEEP settings have an association with outcome in patients with ARDS due to COVID–19;
4. That use of early prone positioning has an association with outcome in patients with ARDS due to COVID–19; and
5. That use of awake prone positioning has an association with outcome in non–intubated patients with acute hypoxemic respiratory failure due to COVID–19.

The first hypothesis was tested in a national observational study presented in **Chapter 2**. The second hypothesis was tested in one international, and in one national observational study, respectively presented in **Chapter 3** and in **Chapter 4**. The third hypothesis was tested in one single–center investigation, and in one national observational study discussed in **Chapters 5** and **6**. The fourth and fifth hypotheses were tested in two national observational studies presented in **Chapter 7**, **Chapter 8** and **Chapter 9.**

In **Chapter 2** we report the results of an observational study including 109 patients with acute hypoxemic respiratory failure due to COVID–19; of them, 33 patients received oxygen support in the form of HFNO, and 76 received invasive ventilation. For the diagnosis of ARDS, we used an adjusted definition in patients under HFNO and the original Berlin definition in patients ventilated with PEEP. In the HFNO group, the requirement of 5 cm H_2O PEEP was replaced by a minimum level of 30 L/min. For mortality risk assessments, we created tertiles of PaO_2/FiO_2 in patients under HFNO, and we used the PaO_2/FiO_2 cutoffs as proposed in the Berlin definition in patients under invasive ventilation, to create groups of patients with mild, moderate or severe ARDS. Clinical endpoints of interests were 28–day mortality, epidemiological characteristics, and ICU– and hospital–mortality. We hypothesized that use of the Berlin definition for ARDS results in comparable patient groups with respect to demographics, baseline characteristics, and outcomes. The P/F ratio of the HFNO group was significantly lower from the start of ICU admission between the HFNO group and mechanical ventilation group which results in more severe ARDS following the Berlin criteria.

Our findings suggest that the adjusted definition for ARDS in which a minimum level of PEEP is replaced by a minimum level of air flow in patients under HFNO results in comparable groups and mortality of patients with COVID–19 pneumonia. However, severity classification using PaO_2/FiO_2 is not possible in patients under HFNO, probably because of the much lower and skewed distribution of the PaO_2/FiO_2 ratio in these patients. Of note, in these patients the median PaO_2/FiO_2 was much lower than in patients ventilated with PEEP.

Chapter 3 contains the results of an international multicenter observational study. In this study, we 'RALE–scored' 350 CXRs in 139 COVID–19 ARDS patients. First, we determined the prognostic capacity of the RALE score of the first CXRs after start of

invasive ventilation. Then we determined the prognostic capacity of changes in the RALE score using all CXRs obtained within the first 14 days of invasive ventilation. The primary endpoint was 90–day mortality; one secondary endpoint was successful liberation from the ventilator. We hypothesized that the RALE score has prognostic capacity in COVID–19 ARDS patients. The RALE score of the baseline CXR was high, and not different between survivors and non–survivors. The RALE score of the baseline CXR after start of invasive ventilation was neither associated with 90–day mortality, nor with the probability of successful liberation from the ventilator. However, an increase in the RALE score over the first 14 days of invasive ventilation days had an association with a higher mortality. We concluded that the RALE score of the baseline CXR after start of invasive ventilation has no prognostic value, but that an increase in RALE score over the first 14 days of invasive ventilation has an association with a higher mortality.

In **Chapter 4** we report the results of a multicenter observational study. In this study, performed in the Amsterdam University Medical Centers, location AMC and VUMC, Amsterdam, The Netherlands, we compared the scores for CXR with lung CT scan abnormalities within the first 14 days of invasive ventilation in COVID–19 ARDS patients. The primary endpoint was ICU mortality. Secondary endpoints were duration of ventilation in survivors, and length of stay in ICU, and hospital–, 28–, and 90–day mortality. We hypothesized that the RALE score and the CT severity score have a comparable prognostic value for ICU mortality. A total 82 CXRs and 82 chest CT scans were scored in 82 invasively ventilated patients with acute hypoxemic respiratory failure due to COVID–19. The RALE score was comparable between survivors vs. non–survivors; the CTSS was lower in survivors compared to non–survivors. The RALE score had no association with ICU mortality and no prognostic capacity. Conversely, the CTSS had a significant association with ICU mortality. However, the prognostic capacity of the CTSS was poor. We concluded that the CTSS was associated with mortality but had a poor prognostic capacity, while the RALE score did not show an association with outcome. CXR-based and CT-based assessments of the extent of lung injury should not be used interchangeably for prognostication purposes.

In **Chapter 5** we present the findings of a single center observational study in critically ill invasively ventilated COVID–19 ARDS patients. We used the data of 28 patients with ARDS due to COVID–19 that received a lung CT scan at low PEEP, i.e., the PEEP level that was used before the CT–scan, and at PEEP of 20 cm H_2O after

a recruitment maneuver. The primary endpoint of this study was the percentage of reaerated nonaerated lung tissue after recruitment maneuvers and ventilation at high PEEP. We hypothesized that invasively ventilated COVID–19 ARDS patients frequently have lung consolidations that can be reaerated. The main finding of our study was that the majority of the critically ill invasively ventilated COVID–19 ARDS patients showed substantial reaeration of lung consolidations after recruitment and ventilation at high PEEP. We concluded that invasively ventilated COVID–19 ARDS patients frequently have collapsed lung tissue that can be reaerated with high PEEP after a recruitment maneuver. This means that high PEEP after a recruitment maneuver can be considered patients with refractory hypoxemia.

Chapter 6 shows the results of one analysis of a multicenter, observational cohort study undertaken in 22 ICUs in the first wave of the national COVID–19 outbreak in the Netherlands, named the 'Practice of Ventilation in patients with COVID–19' (PRoVENT–COVID) study (38). In a propensity matched analysis, we compared 933 invasively ventilated COVID–19 ARDS patients that were categorized as having received invasive ventilation with either a higher or a lower PEEP strategy. The aim of this study was to compare patients ventilated with a higher PEEP strategy to patients ventilated with a lower PEEP strategy with regard to important clinical outcomes. The primary endpoint was the number of days free from the ventilator and alive at day 28 (VFD–28). Secondary endpoints included the incidence of acute kidney injury (AKI), use of renal replacement therapy (RRT), and ICU–, hospital–, and 28– and 90–day mortality. We hypothesized that a higher PEEP strategy is superior to a lower PEEP strategy. In the unmatched analysis, the higher PEEP strategy had no association with the median number of VFDs. However, patients in the higher PEEP group needed RRT more often than patients in the lower PEEP group. In the matched analysis, the higher PEEP group had less VFD–28. Furthermore, patients in the higher PEEP group developed AKI and received RRT more often than patients in the lower PEEP group. Of note, mortality rates were not different between the higher and lower PEEP groups. We concluded that a higher PEEP strategy does not confer clinical benefit in invasively ventilated COVID–19 ARDS patients.

Chapter 7 contains the results of another analysis of the above–mentioned PRoVENT–COVID study. For this analysis, we used the data of the 734 ICU patients of whom 438 received early prone positioning. The aim of this study was to investigate the incidence and practice of early prone positioning in the first wave of the national

outbreak in the Netherlands. The primary endpoint was 28–day mortality. We hypothesized that early prone positioning is used often in these patients, and that its use has an association with outcome. Patients were categorized into 4 groups based on presence or absence of an indication for early prone positioning, and use of early prone positioning. The incidence of early prone positioning was higher in patients with an indication for this intervention, but interesting early prone positioning was also frequently used in patients that had no indication. Duration of prone positioning sessions was longer in patients with an indication than in patients without an indication for prone positioning. We concluded that there was no difference in mortality at day 28 but there was a difference in mortality at day 90. Furthermore, prone positioning was often used and sessions lasted long in invasively ventilated COVID–19 ARDS patients, even in patients without an indication for this intervention.

In **Chapter 8** we describe the rational of another multicenter, observational cohort study, in 16 ICUs in the second wave of the national outbreak of COVID–19 in the Netherlands, named the 'Practice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019' (PRoAcT–COVID) study. We planned to collect data of at least 1.000 ICU patients with COVID–19 pneumonia, to investigate the practice of adjunctive and supportive treatments, and their associations with outcome, in critically ill COVID–19 patients. In **Chapter 9** we report the results of the first findings of this study. In this analysis we investigated the incidence, timing, frequency and duration of awake prone positioning in non–intubated patients, and the associations of this intervention with need for invasive ventilation and mortality. The primary endpoint was a combination of the incidence, timing, frequency and duration of awake prone positioning. The secondary endpoint was a combined endpoint of mortality at day 28 and escalation of respiratory support to invasive ventilation in patients that were initially supported without invasive ventilation. We hypothesized that there is substantial variation in use and practice of awake prone positioning with an association with the need of escalation of respiratory support to invasive ventilation and mortality. Awake prone positioning was applied in 88/546 (16.1%) patients. High–flow oxygen therapy (HFNO) was the most often used oxygen interface. Patients were placed in awake prone position for median 1 (0 to 2) days after ICU admission and median 12.0 (8.4–14.5) hours per day. In the unmatched analysis, treatment failure occurred more often in patients that received awake prone positioning. However, in the matched analysis, this difference was no longer

statistically significant. ICU length of stay and hospital length of stay was significantly longer in the awake prone group than in the standard care group. We concluded that awake prone positioning was used in one in every six patients. Awake prone positioning had an association with treatment failure, an association that was mainly driven by a higher intubation rate.

In the next chapter, the findings of the studies presented in the **chapters 2** to **9** will be placed within a broader context.