Unraveling hypercoagulability in covid-19 and optimizing vte management in the frail nursing home population

Impact paragraph

In this chapter, the relevance of the results described in his thesis and the clinical, economic and societal impact will be discussed. A large part of this thesis was written during the subsequent SARS-CoV-2 waves that the Netherlands have endured and was a direct result of the clinical challenges experienced. We aimed to shed light on this (at the time) new virus and its associated thrombo-embolic complications in an attempt to contribute to improving outcomes for COVID-19 patients in our care. In this context, it is important to realize that global scientific efforts have led to great medical advances with regards to treatment and characterization of patients with COVID-19. This means that part of the evidence presented in this thesis, although at the time of its publication seen as new evidence, may have been outdated or is, by now, accepted as common knowledge.
In the early pandemic predominantly frail and older patients in the nursing homes were most severely affected by the disease. Therefore, in addition to thromboembolic complications in hospitalized patients with COVID-19, we also explored the topic of thromboembolic complications in the frail and, in research, underrepresented nursing home population.

Clinical impact

As part of a global effort to assess the impact of COVID-19, multiple studies have described the incidence and prevalence of venous thromboembolism (VTE) in patients with COVID-19.[1-4] Most literature however, focused on the critically ill ICU population whereas in this thesis we described the (high) prevalence of VTE in different settings. At the time there was very little data on the prevalence of VTE in the non-ICU population, we showed that VTE is not exclusively a problem for ICU patients but that the prevalence is also very high in patients presenting at the emergency department and patients admitted to regular wards. More importantly we found that respiratory deterioration was a marker of pulmonary embolism (PE). This finding of respiratory deterioration proved to be a clinically relevant parameter for clinicians and also ensured optimal use of CTPA whilst minimizing unnecessary patient transport by selecting those patients with high a priori probability of PE. We raised awareness amongst clinicians thereby increasing chances for timely treatment of PE in COVID-19 patients admitted.
The strong association between COVID-19 and VTE raised the obvious question of whether or not anticoagulants would protect against VTE. We saw a trend towards lower mortality in nursing home residents with COVID-19 using antithrombotic therapy. And in the general population we showed that pre-existent use of VKA lowered mortality during the first COVID-19 wave. We can conclude that anticoagulants may have a positive effect on survival in patients with COVID-19. However, it is to be noted that our studies took place during the first COVID-19 wave in the Netherlands when

morbidity and mortality is thought to have been higher than in any of the subsequent waves. It is unsure of whether or not results are reproducible for subsequent waves and under different circumstances (different virus mutations, vaccine status).

The large proportion of excess deaths in the nursing home population during the COVID pandemic highlighted the importance of antithrombotic treatment and the general lack of evidence for pharmacological prevention of venous thromboembolism in the nursing home population. This opens up new research opportunities and collaborations for work towards potentially preventing morbidity and mortality in this patient group, whereby preservation of quality of life should be emphasized.

Economic impact

The economic impact of the COVID-19 pandemic is evident. Although a large part of the economic impact is caused by societal disruption due to lockdown measures and the need for self-isolation in combination with high percentages of sick-leave, it is becoming clear that long-COVID will also have economic impact. Several studies, including our own have shown that persistent coagulation abnormalities are common in a COVID-19 infection. It is this systemic vascular inflammation and dysfunction, partially caused by thrombosis, that is thought to be a key factor driving the various complications of long-COVID.[5] Evidently, thromboembolic complications have been an important focus of this thesis and preventing thromboembolic complications could ultimately help ease the economic impact of COVID-19 by decreasing the number of complications before and during hospital admission. It will also likely decrease the prevalence of long-term morbidity caused by long-COVID. Conclusively, the economic impact of preventing thromboembolic complications in COVID-19 patients, although hard to quantify, is expected to be significant.

So far, studies evaluating the economic burden of thrombosis were mainly hospital based and used a variety of study designs, methodologies, and data sources, making it challenging to compare data across studies.[6] No studies so far have evaluated the economic impact of thromboembolic complications in the nursing home setting. Obviously, it is not possible to extrapolate these hospital data to the nursing home population. It is, however, evident that costs for treatment of thrombosis are considerable and have increased over time. Although, clinical studies have shown that pharmacological prevention in other settings is cost-effective; it has yet to be determined whether or not the same is true for the high-risk nursing home population. Keeping in mind the lack of literature on the pharmacological prevention of VTE in the nursing home setting; the first research priority should be to initiate trials to evaluate efficacy and safety of thromboprophylaxis in this setting. Especially, the reduction of morbidity should be an important aspect as it is closely linked to health-related quality of life. If and when efficacy and safety of thromboprophylaxis in the nursing home

setting is proven, we can then turn our attention to cost-effectiveness of thromboprophylaxis in the nursing home setting.

Scientific impact

The topic of coagulopathy is of great importance in improving outcomes for COVID-19 patients. In this thesis we showed that in COVID-19 patients there is persistent hypercoagulability and hypofibrinolysis. This information is useful for both clinicians and researchers globally as it represents “a piece of the puzzle” for the explanation of the pathophysiological mechanism behind thromboembolic complications. Unraveling the pathophysiology will ultimately contribute to identification of the optimal anticoagulant strategy for COVID-19 patients. Additionally, Rotational Thromboelastometry (ROTEM) currently has limited clinical applications. We managed to implement this relatively labor-intensive laboratory measurement during the first COVID-19 wave, showing that larger scale implementation is possible. Thereby opening up the possibility of future research in other septic pathologies.

The high incidence of thromboembolic complications associated with COVID-19 has raised the obvious question of whether or not anticoagulant therapy would be effective in preventing thromboembolic complications in COVID-19. This thesis presents studies assessing this question by researching the effect of pre-existent anticoagulant therapy in different populations. We have identified (although not statistically significant, but also maybe underpowered) lower mortality rates in anticoagulated patients in the nursing home population as well as in the anticoagulated general population. These figures may be used to design larger (randomized) clinical trials in order to find the optimal and tailored antithrombotic strategy for each patient category. For example, the execution of a future trial comparing thromboprophylaxis to usual care among high-risk nursing home residents.

An important result of the COVID-19 pandemic was that many different disciplines were at the same time faced with the impact of the pandemic on their daily work and life. Another consequence of the urgent situation was the of sudden lack of bureaucracy. This, together with the feeling of great urgency has led to a great willingness to work together and share knowledge in order to improve the acute situation at hand. Studies that would otherwise have been very hard to realize, were made possible by data sharing and collaboration between several hospitals, nursing homes and other organizations. The scientific impact of these new collaborations is not to be underestimated as it opens up endless possibilities for future research projects that supersede the local hospital environment.

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