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The value of artificial intelligence for the treatment of mechanically ventilated intensive care unit patients: An early health technology assessment

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ABSTRACT

Purpose: The health and economic consequences of artificial intelligence (AI) systems for mechanically ventilated intensive care unit patients often remain unstudied. Early health technology assessments (HTA) can examine the potential impact of AI systems by using available data and simulations. Therefore, we developed a generic health-economic model suitable for early HTA of AI systems for mechanically ventilated patients.

Materials and methods: Our generic health-economic model simulates mechanically ventilated patients from their hospitalisation until their death. The model simulates two scenarios, care as usual and care with the AI system, and compares these scenarios to estimate their cost-effectiveness.

Results: The generic health-economic model we developed is suitable for estimating the cost-effectiveness of various AI systems. By varying input parameters and assumptions, the model can examine the cost-effectiveness of AI systems across a wide range of different clinical settings.

Conclusions: Using the proposed generic health-economic model, investors and innovators can easily assess whether implementing a certain AI system is likely to be cost-effective before an exact clinical impact is determined. The results of the early HTA can aid investors and innovators in deployment of AI systems by supporting development decisions, informing value-based pricing, clinical trial design, and selection of target patient groups.

1. Introduction

In the last decade, there has been a growing interest in artificial intelligence (AI) throughout different scientific disciplines. In the medical field the potential of AI was recognised by many researchers [1-3]. Whereas applications of AI have been proposed in all levels of healthcare, intensive care units (ICU) are particularly suitable for the application of AI systems [4-7]. Firstly, since the critical status of ICU patients requires rapid decision making and ideally, changes in health states are anticipated and acted upon promptly [8]. Moreover, due to the continuous monitoring of these critically ill patients, large volumes of complex data are generated [4,9]. AI tools can process and analyse these large volumes of complex data and can provide ICU medical staff with treatment recommendations, predictions on health states, or a decision support system [7,9]. However, the direct clinical and financial consequences of such models often remain unexamined [10,11].

As mentioned above, some AI medical research has focused on mechanically ventilated ICU patients. Examples include decision support systems for mechanically ventilated patients, the detection of patient ventilator asynchrony, predictions of initiation and weaning of mechanical ventilation and the prediction of complications in mechanically ventilated ICU patients [12]. After successful implementation, such AI

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systems can potentially personalise mechanical ventilation, aid decision processes and consequently improve the quality of care [12]. For instance, in patients with sepsis, the prediction of onset 4 h earlier may lead to the timely administration of antibiotics, which can significantly reduce the in-hospital mortality [13,14]. In addition, the patients' health after discharge might also be affected by the adjustments in the treatment regimen. Previous research has found that the quality of life after discharge is related to the duration of mechanical ventilation [15]. Each additional day of mechanical ventilation increases the odds of being moderately to severely disabled[1] six months after ICU discharge with 4% [15].

Hence, despite the limited amount of information available it is plausible that well developed AI systems for mechanically ventilated ICU patients have both a short as well as a long-term (i.e., post-discharge) impact on patient outcomes and finances. However, the exact extent to which AI impacts these outcomes is yet to be determined and the majority of the AI systems studied is never implemented in clinical practice [11]. An early health technology assessment (HTA) could examine the possible impact of such a system before actual implementation by using available data and simulations. In an (early) HTA explicit methods are employed to evaluate the value of a technology across its lifecycle in a multidisciplinary manner [16]. This early assessment can consequently aid investors and innovators in deployment by supporting development decisions, informing a value-based price range, selection of target patient groups, and informing clinical trial design. Technologies can be examined from various perspectives, including medical, economical, social, organisational, legal, and ethical viewpoints [17]. In line with other studies, we adopted a health-economic perspective [18,19]. To this end, we developed a generic health-economic model for early HTA of AI systems for mechanically ventilated ICU patients. This model will estimate the potential cost-effectiveness of AI systems for this patient group across a wide range of clinical settings.

We will illustrate the use of this model in a German setting using an example of an AI system for COVID-19 ICU patients called the Sandman.ICU. The Sandman.ICU collects data from various sources, such as ventilators and electrical impedance tomography and will process these data in real-time using AI to aid clinical decision making. At the time of writing, the data collection for the Sandman.ICU is ongoing and the AI systems based on these data are yet to be finalised and implemented. An example of an AI system would be an alarm that would notify the clinician that a patient is at increased risk for sepsis. The primary aim of the Sandman.ICU is to cause a relevant reduction in the ICU mortality rates. Secondary aims include improvements in patient safety, durations of hospitalisation and mechanical ventilation, patient and staff satisfaction, economic benefits (e.g., cost reductions), and reductions in adverse events. Hence, the final goal is to markedly improve the standard of care in ICUs for COVID-19 patients. However, since the AI models of the Sandman.ICU are yet to be implemented, no clinical trials have been performed and consequently none of these aims have been validated so far. Using our early HTA-approach, we will demonstrate how one can explore the cost-effectiveness of AI systems for mechanically ventilated ICU patients at such an early stage of development.

2. Material and methods

2.1. Cost-effectiveness models

To determine the cost-effectiveness of an AI system for mechanically ventilated ICU patients we developed a generic health-economic model. Health-economic models simulating potential scenarios based on real-world data are commonly used as part of HTA to compare the effects of different health care interventions on the long term. Interventions are usually compared in terms of health consequences as well as economic consequences. By combining these two outcomes one can make informed health care decisions on the possible advantages of different interventions, i.e., whether the intervention is likely to be cost-effective. Using models that simulate disease-specific states experienced by patients, novel interventions are compared to the current standard of care. These states are valued health wise as well as cost wise. By simulating patients to move through the health states, they accrue costs and life years corrected for quality of life (quality-adjusted life year; QALYs) in each of the states. The average costs and QALYs resulting from the simulation then inform the cost-effectiveness outcome. In the next section we will further elaborate on the specific details of our model.

2.2. The model

The generic health-economic model simulates the hospitalisation trajectory of 1000 mechanically ventilated ICU patients. We assumed that during the hospitalisation all patients stayed in the ICU and general ward for part of their hospital stay. Moreover, we assumed that all patients are mechanically ventilated at a certain point during their hospitalisation although not full-time. The order in which the patients are admitted to the different departments during their hospitalisation can differ between patients and is not specified in the model. We simulated patients for a lifetime, i.e., starting from their hospitalisation until their death, which can either be during the hospitalisation, during their recovery after discharge from the hospital, or based on their life expectancy.

Notably, the proposed generic health-economic model is a slight variation on a traditional Markov model in which a cohort moves through different health states with a prespecified cycle time. Instead, in the proposed generic health-economic model the health states vary in duration. The model consisted of four different health states, the hospitalisation state, a recovery state, a post-recovery state, and a death state. All patients start in the hospitalisation state. The hospitalisation state has three substates, namely the general ward, the ICU, and the ICU with mechanical ventilation. All patients remain in each of these three substates for a prespecified length of stay. From the hospitalisation state patients can move either to the recovery state or to the death state. The recovery state takes a maximum of six months, that is starting from discharge until 180 days after hospital admission. The recovery state consists of two substates, namely 'not to mildly disabled' or 'moderately to severely disabled'. Patients are in either of these two substates. The 'moderately to severely disabled' substate could be viewed as post-intensive care syndrome [15]. The probability of being moderately to severely disabled is dependent on the duration of mechanical ventilation. A percentage of patients moves from the recovery state to the death state and the timing of this transition differs per person. All surviving patients move to the post-recovery state. From the post-recovery state patients move to the death state after their expected lifetime. The death state is an absorbing state, patients can enter this state from all health states, but can never leave this state.

The proposed generic health-economic model was conceptualised using literature research and developed within the ENVISION consortium by health economists (LRZ, SvdP, ADIvA, MJP) [20]. Moreover, it was adjusted and validated by anaesthesiologists/ICU clinicians (KZ, JK, BF) and was examined by an external review panel both during and post development. Final validation was performed using extreme value testing. The model was implemented in R version 4.2.1 [21]. A graphical overview of the generic health-economic model can be found in Fig. 1.

2.3. Outcomes

Four different outcomes were used to assess the cost-effectiveness of an AI system compared to care as usual. First, we assessed the incremental costs. Second, we assessed the incremental QALYs. Next, using

[1] Defined as having a World Health Organisation's Disability Assessment Schedule (WHODAS II) score above 25%

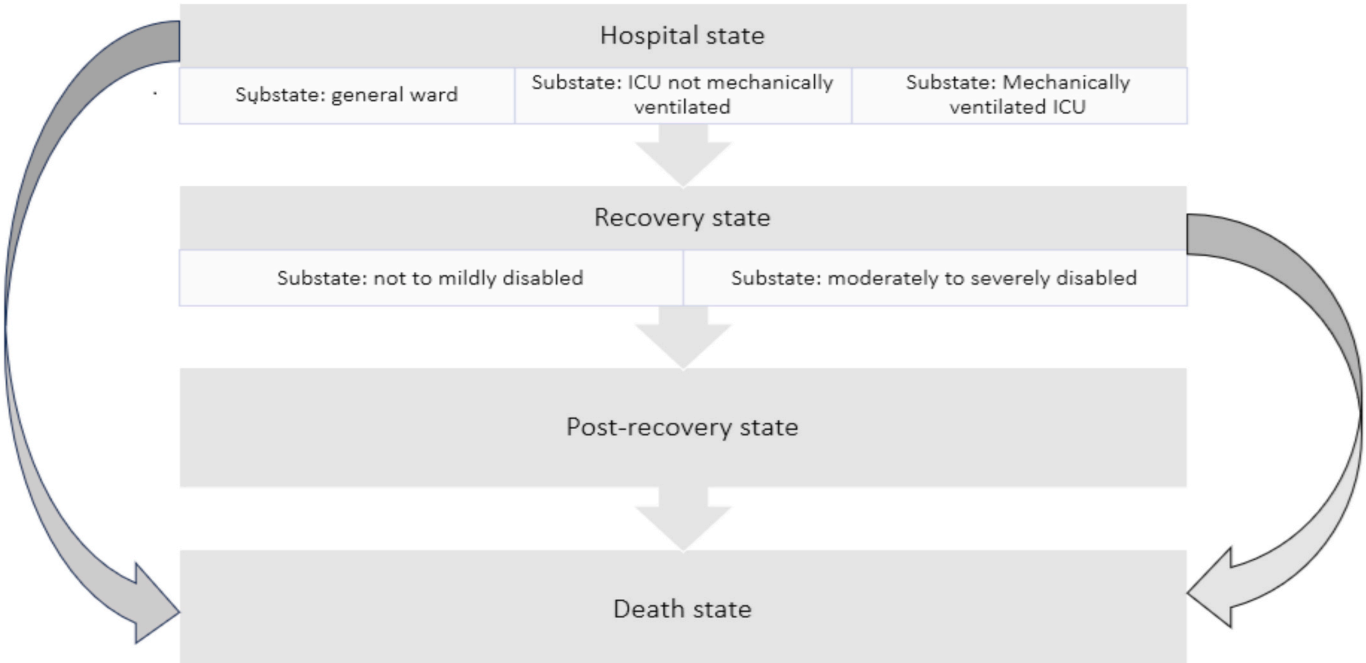

Fig. 1. Overview of the generic health-economic model.

the incremental cost-effectiveness ratio (ICER), we assessed the costs per QALY (see Appendix Eq. 1). This was subsequently compared to the amount an HTA-agency or society is willing to pay for a QALY, referred to as the willingness-to-pay threshold (WTP). Finally, the incremental net monetary benefit (NMB) was assessed. The incremental NMB converts the health benefits, that is the incremental QALYs, to a monetary value using the WTP threshold and compares this to the incremental costs of the treatment [22]. The formula for the incremental NMB can be found in Appendix, Eq. 2. An intervention is considered cost-effective when the incremental NMB is positive. We used a WTP of €30,000 per QALY. However, we also explored other values of the WTP i.e. €50,000 and €80,000 per QALY.

2.4. Illustration of the generic health-economic model

To demonstrate the generic health-economic model, we assessed the cost-effectiveness of the Sandman.ICU in Germany. In this section and the following sections, we will discuss the parameters used in the early HTA of the Sandman.ICU. While some of these parameters are rather specific, others might be applicable to other AI systems as well. Parameters that are unsuitable for a specific AI system can easily be adjusted to perform an early HTA of other AI systems, other patient groups or other regions.

2.4.1. The parameters

Parameters for this example were mostly obtained from the literature. Firstly, we assumed that at the start of the model all patients were 63 years old, which is the average age of 386 mechanically ventilated COVID-19 patients from the beginning of the COVID-19 pandemic until mid-2021 in a German costing study [23]. 37.49% of all patients in our model were female, which was obtained from a large study involving 137,750 German ICU COVID-19 patients. In accordance with the literature an in-hospital mortality of 33.36% was used [24]. All patients remained in each of the hospitalisation substates for the mean length of stay (LOS). The mean LOS and standard deviations of LOS were acquired using the aforementioned costing study [23]. Of all patients discharged from the hospital alive, 24.81% was assumed to be moderately to severely disabled in the recovery state [15]. We assumed that this percentage of moderately to severely disabled people was applicable for the mean duration of mechanical ventilation, which was estimated at 4.6 days [15]. Moreover, according to this study, each extra day of mechanical ventilation led to an increase of 4% in the odds of being moderately to severely disabled [15]. Additionally, in a single centre study 405 patients from the 6518 COVID-19 patients discharged alive from the hospital (= 6.2%), died within six months after their initial hospital admission [25]. Hence, in accordance with the literature a total of 6.2% of the patients deceased in the recovery state. Moreover, the mean survival time for these patients was approximately 16 days after discharge [26]. Next, all surviving patients were assumed to be fully recovered six months after hospital admission and resumed their life until they reached their life expectancy (corrected for sex). Finally, we valued present life years higher compared to future life years by discounting with a 3% discount rate [27,28]. For an overview of all parameters, we refer to Table 1 in the Appendix.

2.4.2. Intervention

As previously mentioned, the goal of the Sandman.ICU is to markedly improve patient care compared to care as usual, which is manifested as several envisioned clinically relevant endpoints. Since the early HTA of the Sandman.ICU is meant as an example of the possible type of analysis and outputs generated with our proposed generic health-economic model, we opted for a concise approach focusing on two of the envisioned endpoints of the Sandman.ICU. To understand the upper limits of the potential benefits we assumed that the Sandman.ICU had an accuracy of 100%. In our example we assumed that on average, the Sandman.ICU reduces the in-hospital mortality rate by 1% and the duration of mechanical ventilation with 4 h. Both these parameters were based on clinical assumption (JK and BF). We assumed that the AI system does not have any negative impacts. For other AI systems, the above parameters can be adjusted based on literature, data analysis or expert opinion. For instance, mortality intervention effects of an AI system with a specific sensitivity and specificity can be estimated using the methods discussed in the study of Calvert et al. [29]. In addition, other parameters might also be affected by the proposed AI system and these can be adjusted relatively easily.

2.4.3. Costs for the AI system

An important characteristic of costs for an AI system in a health-economic model is that the system will have fixed costs regardless of whether there will be any eligible patients. In our example, we assumed that the Sandman.ICU will be available on all beds with mechanical ventilation, but will only be used for COVID-19 patients who are mechanically ventilated. As the Sandman.ICU only benefits mechanically ventilated COVID-19 patients, the total price per patient and mechanically ventilated ICU day of the Sandman.ICU depends on the German mechanically ventilated COVID-19 ICU occupancy. To obtain this we utilise the average German COVID-19 ICU occupancy in 2022, which was 1518.75 beds [30]. This number was subsequently divided by the most recent number of ICU beds available in Germany published by the *Statistisches Bundesamt* (Statistics Germany) in 2022, which is 26,327 ICU beds [31]. Finally, the result of this ratio was multiplied by 75.7%, which is the percentage of mechanically ventilated COVID-19 patients in Germany [23]. This led to an approximated mechanically ventilated COVID-19 ICU occupancy of 4.4% per year.

Next, we calculated the annual costs of the AI system. We based the costs for the Sandman.ICU on a clinic with 20 mechanically ventilated ICU beds and 20 users (clinical staff) and assumed that the system would last 10 years. Costs consisted of costs for set up and installation, training for the system, hardware, service and remote support and licensing, which totalled up to € 2050 per bed per year [32]. For more details on these costs, we refer to the Appendix Table 2 and Eq. 3.

Subsequently, the costs per COVID-19 patient and mechanically ventilated ICU day can be obtained by dividing the annual costs by the mechanically ventilated COVID-19 ICU occupancy and finally by the number of days per year (see Fig. 2).

2.4.4. Other costs

Costs for each hospital substate were acquired from a study by Zwerwer et al. [23], which estimated the daily costs for each hospital substate using generalised linear models with administrative costing data of 510 ICU COVID-19 patients of the University hospital Frankfurt am Main. Only costs for an additional day in each sub-state were considered, that is disregarding the effect of age, gender, and comorbidities on the costs. Costs for the recovery state were estimated from a Singaporean study [33]. In this study, rehabilitation costs were evaluated for 27 mechanically ventilated COVID-19 ICU patients. The authors found that on average each patient required 17.3 physiotherapy, 6.11 occupational therapy, and 4.81 speech therapy sessions. This was equivalent to a total healthcare cost of € 2281.81 (inflated to 2022 [34], converted to German euros [35]). Next, we assumed that the rehabilitation costs for moderately to severely disabled patients were three times as high compared to the rehabilitation costs for not to mildly disabled patients Finally, we assumed that the simulated patients had no further medical costs related to their COVID-19 hospital admission during the post-recovery state. No discounting was applied to the costs, since we assumed patients only incur costs during the first year of the model.

2.4.5. Utilities

To express health benefits in terms of QALYs, each (sub)state of the model should be assigned a value for quality of life, or utility. The utilities for the hospitalisation substates were calculated using disutilities. These disutilities were subtracted from the utilities in the post-recovery state, which is discussed further on. The disutilities of the different hospitalisation substates were obtained from a study by the Institute for Clinical and Economic Review (2020) on the cost-effectiveness of treating hospitalised COVID-19 patients with Remdesivir [36]. Utilities in the recovery state were obtained from the study of Hodgson et al. (2017), who measured the utilities of not to mildly disabled and moderately to severely disabled post-mechanically ventilated ICU patients using the EQ5D six months after ICU admission [15]. Moreover, utilities in the post-recovery state were taken from the study of Szende et al. (2014) who estimated these utilities using the time trade-off method [37]. They distinguished different utilities for German males and females of different age groups. Hence, we used the gender and the age of the patients in our sample to determine the utility for each patient. Moreover, the utilities were adjusted for ageing of the patients. The obtained utilities were multiplied by the life years in the post-recovery state to calculate the QALYs for patients in this state.

2.5. Base case analysis and one-way sensitivity analysis

All outcomes were evaluated for the base case scenario. This analysis was performed for patients of age 60, 63 and 70 years old. Next, a one-way sensitivity analysis was performed. In a one-way sensitivity analysis, we vary all parameters one at a time until a prespecified boundary and evaluate the effects of this variation on the ICER. As boundaries, we took the 95% confidence interval (CI) when available and otherwise we subtracted and added 10% of the base case value to the base case value (see Appendix Table 1). All population parameters, the life expectancy and the costs of the AI system were kept fixed. The effects on the ICER are shown in a tornado plot, which illustrates the six most influential parameters of the model.

2.6. Probabilistic sensitivity analysis and scenario analysis

Next, we performed a probabilistic sensitivity analysis (PSA). For this analysis all parameters were simultaneously varied probabilistically according to predefined distributions (see Appendix Table 1). In case standard deviations were not available we used 10% of the base case value. We performed a thousand simulations for which we subsequently calculated the incremental QALYs and incremental costs. The incremental NMB was used as the outcome variable. The PSA results were plotted on a cost-effectiveness plane. Next, a cost-effectiveness acceptability curve (CEAC) was created, which shows the probability that the intervention is cost-effective for different values of the WTP threshold (ranging from € 0 to €100,000 per QALY). In addition, we ran the PSA for different treatment costs and mechanically ventilated COVID-19 ICU occupancies. The daily treatment costs ranged from €0 to €600 per mechanically ventilated bed in steps of €5. The mechanically ventilated COVID-19 ICU occupancies ranged from 1% to 100% in steps of 1%. We plotted the mean incremental NMB for the different treatment costs and mechanically ventilated COVID-19 ICU occupancies using a WTP of €30,000, €50,000, and €80,000 per QALY.

Finally, an important characteristic of AI systems implemented in clinical practice is their potential to improve over time. However, recently it has been shown that AI systems can also degrade in performance over time when implemented in clinical practice [38]. Hence, the

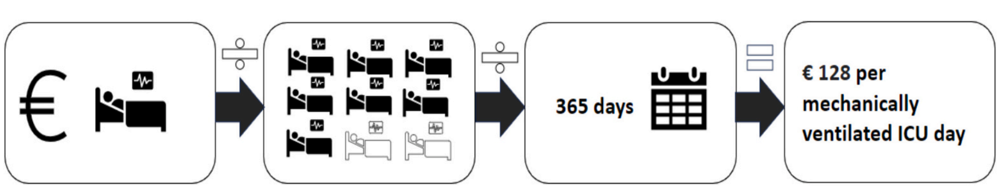

Fig. 2. Calculation of the costs of the AI system per COVID-19 patient and mechanically ventilated ICU day. Costs can be derived by dividing the annual costs of the AI system per bed by the average proportion of mechanically ventilated COVID-19 ICU beds occupied in a year and then dividing this by the number of days per year.

performance of the AI system over time is highly uncertain and depends on the setting, prediction tasks at hand, the implemented model and maintenance of the algorithm. Given this uncertainty in the direct impact of the AI system, our model explores the impact of different treatment effects using a combination of scenario analyses and PSA. Using the PSA, we ran scenario analyses on different intervention effects (i.e., mortality and the duration of mechanical ventilation). The mortality intervention effect was varied between 0% and 5% in steps of 0.1% and the reduction in the duration of mechanical ventilation was varied between zero and one day of mechanical ventilation in steps of 0.03 days. This was performed for a treatment price of €128, which corresponds to a mechanically ventilated ICU occupancy of 4.4%. The mean incremental NMB was plotted in a heatmap for each of these scenarios assuming a WTP of € 30,000.

2.7. Early HTA of other AI systems

Finally, we illustrated how the developed generic health-economic model can be applied to two other AI systems in the literature. Firstly, we explored an AI system predicting sepsis several hours before onset in the ICU [39]. Secondly, we examined an AI system that detects patient ventilator asynchrony (PVA) [40].

3. Results

In this section we will discuss the results of the cost-effectiveness analysis for the Sandman.ICU. This is meant as an illustration of the possible type of analysis and outputs generated with the proposed generic health-economic model. It can be noted that the generic health-economic model provides a workable environment to allow early HTA where remaining gaps in knowledge can be addressed by expert opinion and assumptions.

3.1. Base case

In the base case, the Sandman.ICU is cost-effective for all estimated ages when assuming an intervention effect of 1% mortality reduction, a reduction of 4 h in mechanical ventilation and a WTP of € 30,000. The base case results can be found in Table 1.

3.2. One-way sensitivity analysis

The Tornado plot showing the effect of varying the different parameters on the ICER can be found in Fig. 3. The one-way sensitivity analysis showed that the most influential parameters in the model are the mean duration of mechanical ventilation, the intervention effect on the in-hospital mortality and on the duration of mechanical ventilation, and the utilities during the post-recovery state. The higher the mean duration of mechanical ventilation, the higher the ICER. Moreover, lowering the intervention effects and the utilities during the post-recovery state also leads to a higher ICER.

3.3. Probabilistic sensitivity analysis

The mean results of the PSA show that the usage of the Sandman.ICU

Table 1
Results of the base case.

Age	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)*
60	1024	0.15	6885	3438
63	1024	0.14	7581	3029
70	1024	0.10	10,300	1959

* Assuming a willingness to pay € 30,000. QALY: Quality adjusted life year.

for mechanically ventilated COVID-19 patients is cost-effective with a mean incremental NMB of €3055. Under the aforementioned parameter settings, one extra QALY costs will cost on average € 7334. All the simulated scenarios in the PSA showed health benefits, that is increased QALYs, and 34.3% of the simulated strategies in the PSA were cost-saving. The results of the PSA are visualised in the cost-effectiveness plane in Fig. 4. All simulations are in either the northeast or southeast quadrant, which implies complete certainty of a positive health effect.

Next, using the results from the PSA, the probability of the Sandman. ICU being cost-effective versus care as usual, was assessed for different WTP thresholds. The results are visualised using a CEAC (Fig. 5). Overall, for a WTP of € 10,000 and above there is a high probability ($\geq$ 72.7%) that the Sandman.ICU is cost-effective. This probability increases for higher WTP and exceeds 95% for WTP of € 40,000 and above.

The mean results of the PSA for different prices and different WTP thresholds can be found in Fig. 6a. Moreover, Fig. 6b shows the mean results of the PSA for different mechanically ventilated COVID-19 ICU occupancies and different WTP thresholds. The plot shows that assuming a WTP of € 30,000, below an occupancy of approximately 1.5%, the Sandman.ICU is no longer considered cost-effective. Moreover, Fig. 6b shows that increasing the mechanically ventilated COVID-19 ICU occupancy beyond 20% has a marginal impact on the incremental NMB.

Finally, Fig. 7 shows the impact of different intervention effects on the incremental NMB. Interestingly, the incremental NMB is positive for the main part of the plot. Hence, the Sandman.ICU appears to be cost-effective for a wide range of intervention effects. However, for some intervention effects, the costs of the Sandman.ICU no longer outweigh the benefits. For instance, in the case of no reduction in the mortality and a reduction of 13.5 h or less in the mechanical ventilation duration, or a reduction in mortality of 0.3% or less and no reduction in the days of mechanical ventilation, the treatment is not considered cost-effective.

3.4. Recommendations to be concluded from the early HTA of the Sandman.ICU

The early HTA in this example shows that even for low mechanically ventilated COVID-19 occupancy the Sandman.ICU will be cost-effective when assuming a mortality reduction of 1% and a reduction in the duration of mechanical ventilation of 4 h. In the current analysis, the price of the Sandman.ICU was dependent on the mechanically ventilated COVID-19 occupancy. Therefore, the daily price of the Sandman.ICU could be highly dynamic. Instead, a fixed daily price per treated patient can be more intuitive for innovators, hospitals, and health care systems. Alternatively, when maintaining the current pricing strategy, broadening the target patient group to for instance ICU patients with respiratory tract infections would lower the price per mechanically ventilated ICU day and consequently increase the probability of the AI system being cost-effective.

3.5. Assessing the cost-effectiveness of other AI systems

Subsequently, we explored how to apply the proposed generic health-economic model to two other AI systems (see Methods). This is meant as an illustration of the possible adaptations of the developed generic health-economic model to other AI systems. To apply the generic health-economic model to the previously mentioned AI system predicting sepsis in the ICU, all parameters such as sex, in-hospital mortality, age, LOS, utilities, and costs in the different hospital (sub)states are to be adjusted to ICU demographics of the respective country for which the analysis is performed. These parameters are used to simulate care as usual. In addition, to simulate the intervention group, the parameters for the intervention have to be adjusted. Firstly, the daily price per ICU bed for the AI system needs to be adjusted based on the price level, currency, and ICU occupancy. Next, the intervention effects, such as reductions in mortality, mechanical ventilation, 30-day mortality and

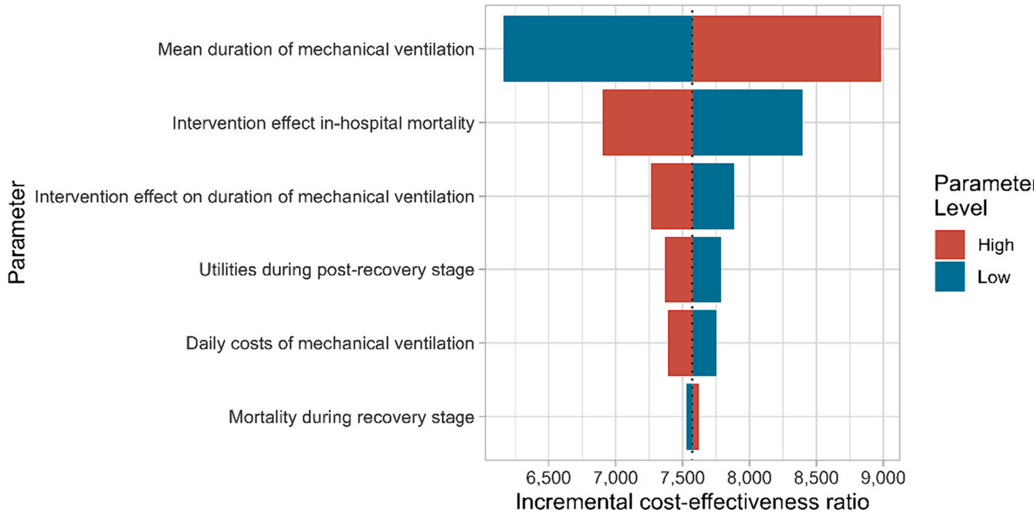

Fig. 3. Tornado plot showing the effects of varying the different parameters on the ICER.

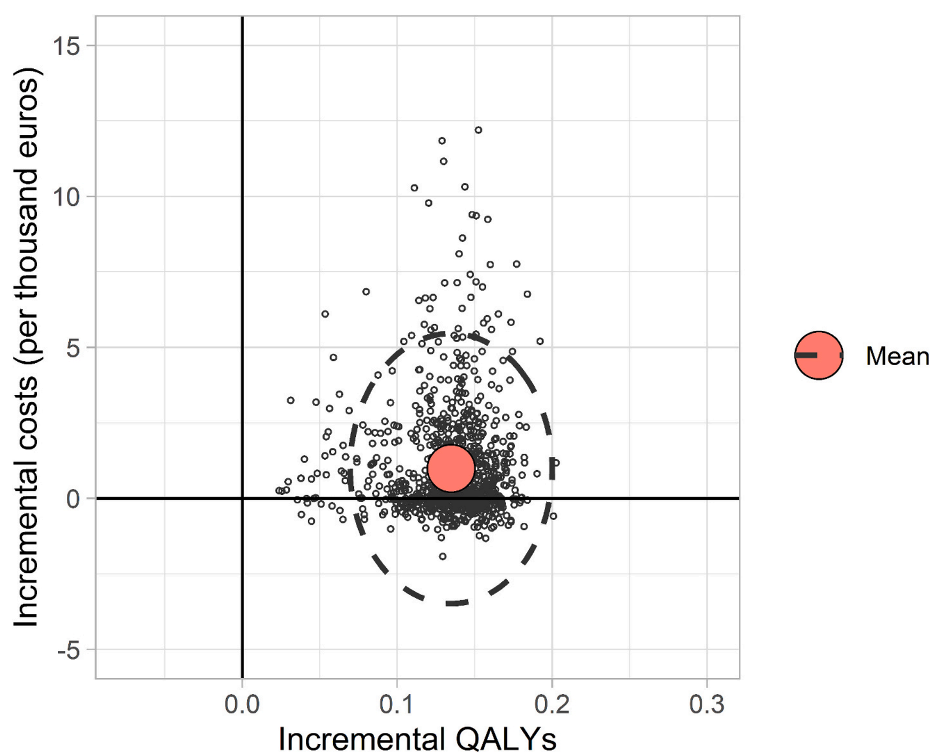

Fig. 4. Cost-effectiveness plane for the Sandman.ICU compared to the current standard-of-care. Visualised are all iterations, the mean of all iterations and the 95% confidence ellipse. All iterations of the PSA are either in the southeast or northeast quadrant.

LOS need to be examined using literature research, statistical analysis, or expert opinion. Consequences of incorrect predictions of the AI system can be included as well. For instance, the effect of incorrect predictions can be assumed to influence the mechanical ventilation duration. Subsequently all these intervention parameters need to be updated in the model. Next, the potential cost-effectiveness of the above AI system is obtained by running the generic health-economic model together with the sensitivity analyses.

To apply the generic health-economic model to the AI system detecting PVA, all parameters in the model must be adjusted to correspond to the demographics of mechanically ventilated patients of the respective country for which the analysis is performed. Furthermore, the daily price per ICU bed for the AI system needs to be adjusted based on the price level, currency, and mechanically ventilated ICU occupancy. Next, the intervention effects need to be assessed and adjusted accordingly. For instance, using literature research, statistical analysis, or expert opinion, the effect of the AI system on hospital LOS and duration of mechanical ventilation can be estimated. Subsequently, simulating the health trajectories for these patients will lead to an early estimate of the cost-effectiveness of this AI system.

4. Discussion

4.1. Main findings

While an increasing amount of AI systems are developed for

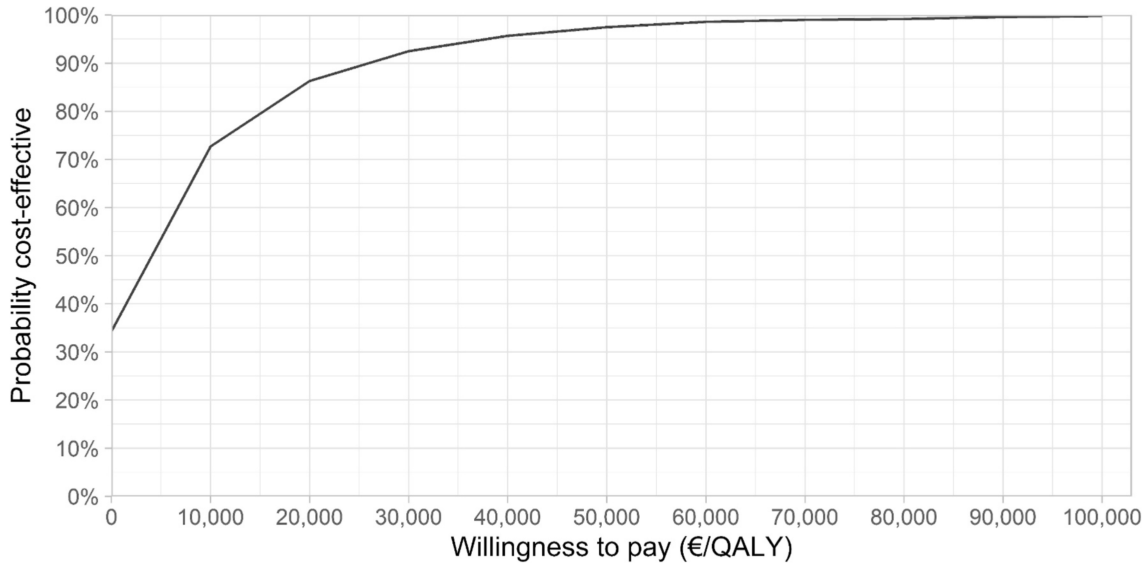

Fig. 5. Cost-effectiveness acceptability curve showing the probability that the Sandman.ICU is cost-effective versus care as usual.

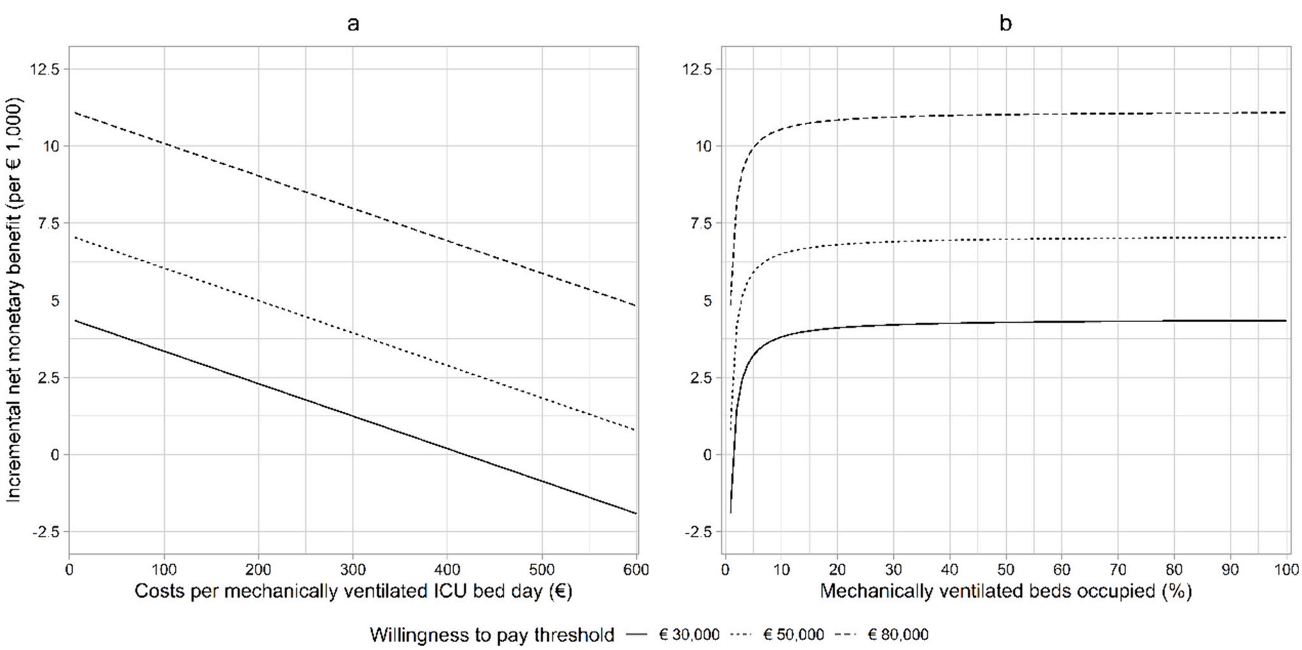

Fig. 6. Incremental net monetary benefit for the Sandman.ICU for different WTP thresholds ranging from € 30,000 to € 80,000 for (a) different prices and (b) different mechanically ventilated COVID-19 ICU occupancies.

mechanically ventilated ICU patients, their financial and health consequences often remain unanalysed [10,11]. In the current study we developed and demonstrated a generic health-economic model estimating the cost-effectiveness of AI systems for mechanically ventilated ICU patients at an early stage of development. By varying input parameters and assumptions, the developed model can examine the cost-effectiveness of AI systems on the ICU across a wide range of different clinical settings. For instance, it can estimate the cost-effectiveness for different prespecified age groups, produce a tornado plot, estimate the probability of being cost-effective for different WTP thresholds, different treatment prices and ICU occupancies, and estimate the cost-effectiveness for varying treatment effects.

To date, as far as we are aware, only two other studies performed an (early) HTA for AI systems in the ICU [41,42]. However, in contrast to our proposed generic health-economic model both these studies do not consider mechanical ventilation in their analysis. Next, whereas other studies assessing the value of AI systems for ICU patients are specific to the respective model and/or patient groups [29,41,42], our proposed generic health-economic model offers a high degree of flexibility and is easily adjustable to other clinical situations, countries, and AI systems, thereby forming a valuable addition to the limited amount of early HTA studies for AI systems in the ICU [19]. Our proposed generic health-economic model can aid investors and innovators by supporting development decisions. For instance, the tornado plot might show that certain intervention effects are highly influential for the cost-effectiveness. Subsequently, the innovators and investors can focus on optimising these intervention effects to maximise the health and financial benefits of the AI system. Next, our generic health-economic model can inform investors and innovators on pricing strategies, value-based pricing, target patient groups and clinical trial design. For instance, the outcome

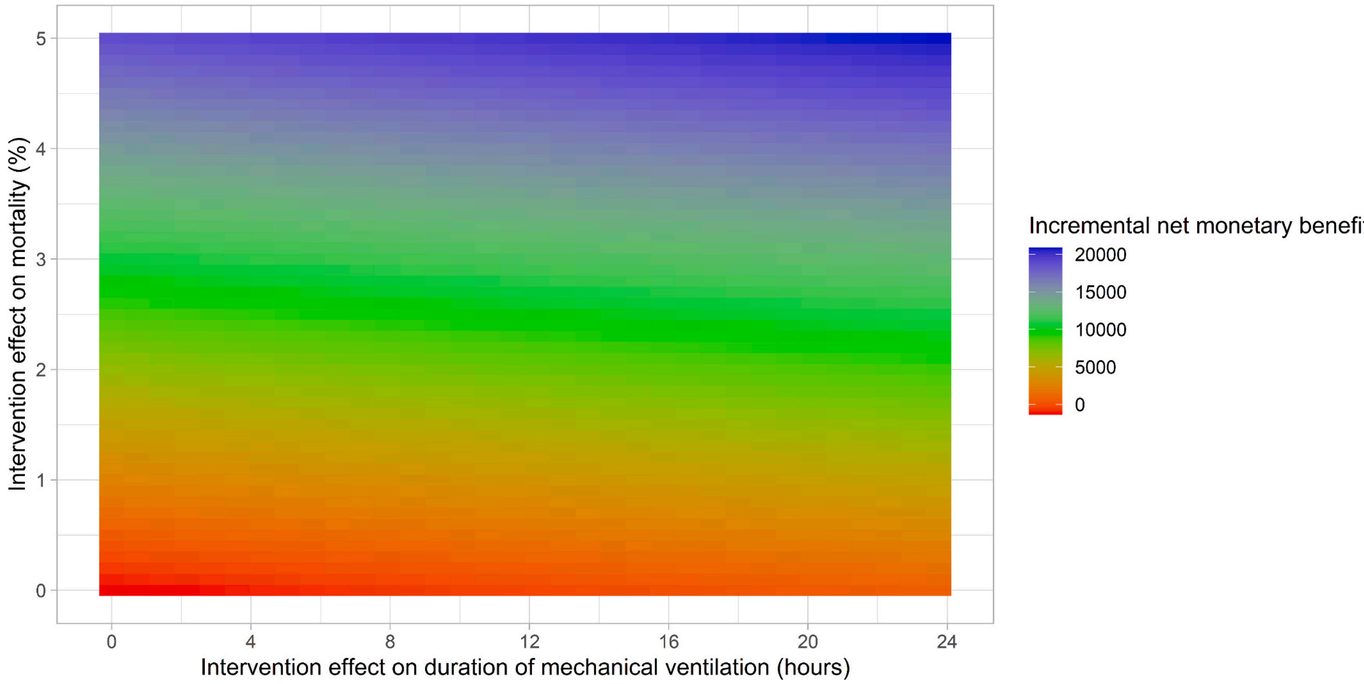

Fig. 7. Heatmap of the mean incremental net monetary benefit for different intervention effects on mortality and duration of mechanical ventilation. Assuming a treatment price of € 128 per mechanically ventilated ICU day and a WTP of € 30,000 per QALY. The x-axis represents the reduction in duration of mechanical ventilation (in hours) and the y-axis represents the reduction in mortality (in percentages). The colour indicates the incremental net monetary benefit.

of the early HTA might show that the AI system is beneficial for a specific patient group. Subsequently, development decisions and clinical trials can be focused on this specific patient group. Finally, recently certain research funding agencies require an economic analysis of a technology before granting research proposals to increase the probability of affordable healthcare [17]. The proposed framework can be used in such situations as well. The generalisability of the proposed generic health-economic model increases the efficiency of these processes by having the model structure and code readily available for a desired early HTA.

Next, when the generic health-economic model is applied to a yet to be developed AI system we recommend adjusting the intervention effects to the target product profile to provide an accurate early HTA. Moreover, when utilising the proposed generic health-economic model, we recommend innovators and investors to involve several stakeholders, such as health economists and ICU clinicians to confirm the correctness of the model in specific (sub-) populations. Finally, involving decision makers in the application or adjustments of the generic health-economic model for specific (sub-) populations can streamline final deployment.

4.2. Limitations and strengths

Our proposed generic health-economic model provides an opportunity to explore the cost-effectiveness of AI systems at an early stage of development, however it does have some limitations. Firstly, the basic structure of the generic health-economic model might oversimplify reality. For instance, in the model, it is assumed that, in the recovery state, the utilities for the quality of life remain stable at the reported utility scores of Hodgson et al. (2017) [15]. However, this may not be a realistic scenario. One would expect the utilities right after discharge to be lower and subsequently slowly increase to the level found six months after ICU admission by Hodgson et al. (2017) [15]. Hence, utilities in the recovery state have potentially been slightly overestimated. Nevertheless, we do not expect this to have an impact on the final results as this is the case for both care as usual as well as the treatment group. Furthermore, the effect of the utilities in the recovery state on the ICER was negligible in the tornado plot. Also, recovery of ICU admission differs per patient and might take longer than six months. For instance, in a Dutch multicentre cohort study including 11 ICUs, almost 75% of the surviving COVID-19 patients reported physical symptoms one year after ICU admission [43]. Hence, assuming sudden recovery at six months is an oversimplification of the reality and probably too optimistic. In addition, from six months after hospital admission onwards the remaining life expectancy for the general population was assumed, while in reality ICU survivors are at increased risk of mortality until 15 years after discharge [44]. Nevertheless, the highest excess mortality is within the first year after discharge [44]. Moreover, the effect of mortality in the recovery state on the ICER was small in the tornado plot. Therefore, we do not expect the results of this study to be much affected by this. Additionally, in our proposed generic health-economic model the probability of disability after discharge is solely impacted by the duration of mechanical ventilation. However, other factors, such as reduced ICU LOS, the specific disease, and improved quality of care, might also have an influence on this. For instance, it has been shown that for COVID-19 patients each day spent extra in the ICU leads to 4.4% higher odds of having a decreased quality of life six months after discharge [45]. Nonetheless, if a treatment is expected to reduce the ICU LOS, the model can be adjusted to include the long-term effect of reductions in the ICU LOS as well. Next, increased quality of care might also influence the duration of mechanical ventilation or ICU LOS. Hence, the effect of improved quality of care is in that case partly covered by our model. Moreover, the model does not consider the effect of a longer duration of mechanical ventilation on the mechanically ventilated ICU occupancy, which should increase and therefore lower the costs of the AI system per mechanically ventilated ICU day. However, as the prediction of future mechanically ventilated ICU occupancy is relatively uncertain, modelling the interplay between the duration of mechanical ventilation and mechanically ventilated ICU occupancy would unnecessarily complicate and potentially overcomplicate the model. To overcome this uncertainty the model thoroughly explores the effect of different mechanically ventilated ICU occupancies on the cost-effectiveness.

Next, the intervention effects in our model are indirect consequences of the implemented AI systems. Direct consequences are often specific to an AI system. Therefore, basing our generic health-economic model on direct consequences would impact the generalisability. Instead, the indirect consequences have to be estimated beforehand as input using for example expert opinion, literature, or statistical analysis of relevant data. The sensitivity analysis would subsequently provide a clear overview of the possible scenarios in case of highly uncertain estimates. Furthermore, no negative impact of the AI system has been included in our generic health-economic model. Whereas in general, AI systems are meant to improve the quality of care, false suggestions of the AI-system might impact the care negatively [46]. However, the negative impact of a wrong recommendation by the AI system is highly dependent on the specific AI system and can therefore not be included as a general part in our generic health-economic model. When applying our generic health-economic model to a specific AI system the model can be adjusted to include the negative impact as well. Next, to date our generic health-economic model is not yet validated with appropriate real-world data.

Finally, we applied the generic health-economic model to the Sandman.ICU to illustrate the possible type of analysis and outputs generated with the proposed generic health-economic model. In this example, input data comes from various sources and was not based on systematic review. Moreover, we did not account for potential issues regarding transferability of data. For instance, utilities were obtained from different continents and derived with different methodologies. Relatedly, costs in the recovery state were obtained by converting total COVID-19 recovery costs reported in a Singaporean study to German euros, without considering the German costs per unit of physiotherapy, speech therapy and occupational therapy. However, in Germany there are no fixed unit costs for these recovery services as patients may opt for either stationary rehabilitation, outpatient settings, or private arrangements.

While the limited complexity of this model can be viewed as a disadvantage it can also be viewed as an advantage. Researchers have recommended earlier to use models that adequately simulate the situation, but have the simplest model structure possible [47]. The simplicity of the model makes the model highly interpretable and easy to use. Moreover, the computational time is relatively low compared to more complicated models and therefore we were able to explore a broad range of scenarios. Additionally, the proposed model structure provides flexibility and most parameters are readily available and can therefore easily be adjusted to the situation in other countries, different treatment options and other diseases. Next, our proposed generic health-economic model offers the opportunity to examine the cost-effectiveness of AI systems at an early stage of development before final implementation. Subsequently, when the treatment price remains identical the heatmap of the incremental NMB (see Fig. 7) can be used to examine the cost-effectiveness of the AI system after more information is available on the final intervention effects. This is especially useful after final implementation in clinical practice since it offers the opportunity to easily examine the cost-effectiveness of the AI system when its performance changes over time. In case of other intervention effects and/or a different treatment price the model can easily be updated and readily provide an estimate of the cost-effectiveness. Therefore, when the AI systems are running in real-time the true cost-effectiveness can easily be examined.

5. Conclusions

The proposed generic health-economic model provides an estimate of the potential cost-effectiveness of AI systems for mechanically ventilated ICU patients when the exact impact of the system is not yet determined. Our generic health-economic model can easily be adapted to various clinical situations and is capable of estimating cost-effectiveness across a wide range of different clinical settings. Moreover, the output of the generic health-economic model can be used to support development decisions. Finally, using the proposed generic health-economic model, investors and innovators can quickly scan the potential cost-effectiveness of implementing a new AI system before implementation.

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CRediT authorship contribution statement

Leslie R. Zwerwer: Writing – review & editing, Writing – original draft, Visualisation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualisation. **Simon van der Pol:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualisation. **Kai Zacharowski:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualisation. **Maarten J. Postma:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualisation. **Jan Kloka:** Writing – review & editing, Project administration, Investigation, Conceptualisation. **Benjamin Friedrichson:** Writing – review & editing, Project administration, Investigation, Conceptualisation. **Antoinette D.I. van Asselt:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualisation.

Declaration of competing interest

Authors LRZ, JK, SvdP, ADIvA and BF have no competing interests to declare that are relevant to the content of this article. MJP reports grants and personal fees from various pharmaceutical industries, all outside the submitted work. He holds stocks in Pharmacoeconomics Advice Groningen (PAG Ltd.; Groningen, Netherlands) and Health-Ecore Ltd. (Zeist/Groningen, Netherlands) and is advisor to Asc Academics (Groningen/Utrecht, Netherlands), all pharmacoeconomic consultancy companies. The Department of Anaesthesiology, Intensive Care Medicine & Pain Therapy of the University Hospital Frankfurt, Goethe University received support from B. Braun Melsungen, CSL Behring, Fresenius Kabi, and Vifor Pharma for the implementation of Frankfurt's Patient Blood Management program. KZ has received honoraria for participation in advisory board meetings for Haemonetics and Vifor and received speaker fees from CSL Behring, Masimo, Pharmacosmos, Boston Scientific, Salus, iSEP, Edwards and GE Healthcare. He is the Principal Investigator of the EU-Horizon 2020 project ENVISION (Intelligent plug-and-play digital tool for real-time surveillance of COVID-19 patients and smart decision-making in Intensive Care Units) and Horizon Europe 2021 project COVend (Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19).

Data availability

The data used in the current study are publicly available. In addition, the R codes of the models are openly available in GitHub at https://github.com/UMCG-Global-Health/eHTA_ICU_AI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154802.

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