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Intelligent plug-and-play digital tool for real-time surveillance of COVID-19 patients and smart decision-making in Intensive Care Units

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Project

Within only six months, over 7.4 million people have been diagnosed with SARS-CoV-2. In the most severely hit countries, more than 10% of infected patients have received treatment in Intensive Care Units (ICUs). Insufficient data and limited knowledge on the disease as well as the lack of tools to support the intensivist in making accurate, timely and informed decisions has led to high mortality rates.

Continuous surveillance, the collection and intelligent analysis of data from many sources, including ventilators and electrical impedance tomography, would allow intensivists to decide on the best suitable treatment to accelerate the recovery of the often comorbid COVID-19 patients, while reducing the burden on clinical staff and healthcare costs. This information would also increase our understanding of the yet unknown course of disease, supporting other stakeholders in the quest for new therapies.

In ENVISION, our multidisciplinary public-private consortium will advance an innovative digital tool, Sandman.MD, a real-time and plug-and-play monitoring app, to an intelligent decision-support system for monitoring, prediction and treatment of COVID-19 patients in ICUs – the Sandman.ICU – reaching Technology Readiness Level 9 and ready for CE marking by the end of the project. The app has been developed by our SME partner app@work and successfully introduced by several hospitals in Germany for use during the perioperative period. Sandman.ICU will be integrated into an AI-driven data analytics suite with predictive modelling tools and enhanced with a smart alert functionality. The digital tool will be validated and demonstrated in 13 hospitals across Europe. Our Health Technology Assessment expert partner will demonstrate the economic and societal value of Sandman.ICU, while an experienced SME will manage the innovation process in view of an immediate market uptake. The rollout will be supported by the European Society of Anaesthesiology and Intensive Care (ESAIC).

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Partner short names

accelCH	accelopment Schweiz AG
GUF	Johann Wolfgang Goethe Universität Frankfurt am Main
ICS-HUB	Institut Catala de la Salut – Bellvitge University Hospital
LMI	Löwenstein Medical Innovation GmbH & Co. KG
UMCG	Universitair Medisch Centrum Groningen
UMCM	Univerzitetni Klinicni Center Maribor
UMFCD	Universitatea de Medicina si Farmacie Carol Davila din Bucuresti

Abbreviations

AI	Artificial Intelligence
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
D	Deliverable
EC	European Commission
ICU	Intensive Care Unit
ICER	Incremental cost effectiveness ratio
H2020	Horizon 2020
LOS	Length of stay
M	Month
MS	Milestone
NMB	Net monetary benefit
OECD	Organisation for Economic Co-operation and Development
PSA	Probabilistic sensitivity analysis
PPP	Purchasing power parities
QALY	Quality adjusted life year
WP	Work Package
WTP	Willingness-to-pay threshold

Executive Summary

As a consequence of the enormous amount of critically ill COVID-19 patients, many academic and corporate researchers were searching for treatments to improve the care for these patients. The application of artificial intelligence (AI) for hospitalized COVID-19 patients to aid clinical decision-making was considered to optimize COVID-19 health care. However, the long-term benefits of such treatment optimizers are rarely discussed. In this deliverable, we are exploring the potential long-term cost savings and health benefits of the implementation of an AI system called Sandman.ICU designed for COVID-19 patients in the intensive care unit (ICU) by means of a health-economic model. The Sandman.ICU is currently implemented in several European ICUs as part of a larger project called ENVISION. The AI system developed during ENVISION collects data from various sources, such as ventilators and electrical impedance tomography. Moreover, it monitors COVID-19 patients in the ICU. The collected data will be processed in real-time using AI and aid clinical decision-making.

To determine the potential health benefits and cost savings of the Sandman.ICU, a highly interpretable health economic model, was developed to simulate a population of 1000 patients with the German clinical setting taken as a base case. As for the time horizon, we used the expected lifetime of the patients. The model consisted of four different stages, the hospitalization stage, the recovery stage, the healthy stage and a mortality stage, following the recommendations of the Sandman.ICU could potentially improve patient care. However, the extent to which patient care improves is currently unknown. Therefore, we assumed that the usage of the Sandman.ICU improves the treatment of COVID-19 patients in the ICU in two different ways, namely by reducing mortality and reducing the duration of mechanical ventilation. Based on the assumed intervention effects, long-term health benefits and costs were calculated using the health-economic model. The health-economic model showed that under the German base case scenario, the treatment with the Sandman.ICU was cost-effective, assuming a willingness-to-pay threshold of € 30,000 per quality-adjusted life year and a daily price of the Sandman.ICU per mechanically ventilated bed of € 120.41. The cost-effectiveness of the Sandman.ICU was explored under a broad range of scenarios. In the majority of these scenarios potential for favourable cost-effectiveness of the Sandman.ICU was illustrated. In case of very low assumed intervention effects or very low mechanically ventilated COVID-19 ICU occupancy, the Sandman.ICU may no longer be considered cost-effective.

Additionally, the cost-effectiveness in other participating countries was explored. Results show that under the aforementioned assumptions, the Sandman.ICU will be cost-effective under a wide set of scenarios for all countries involved in ENVISION.

However, since the algorithms of the final Sandman.ICU are yet to be implemented and the model is based on data retrieved from patient management systems and literature, results need to

be interpreted with caution until more is known about the direct treatment effects of the Sandman.ICU.

1 Introduction

The 11th of March 2020 marks the official start of one of the deadliest pandemics in history; the COVID-19 pandemic (1). At the time of writing, the COVID-19 pandemic caused 662 million infections worldwide and over 6.7 million deaths (2). The huge amount of critically-ill COVID-19 patients disrupted health care majorly and put enormous work pressure on health care workers around the world (3–6). As the number of critically ill patients increased, governments had to impose several measures to prevent the further spread of the virus (5,7,8). In the meantime, many academic and corporate researchers were searching for treatments to improve the care for COVID-19 patients (9,10). The application of artificial intelligence (AI) for hospitalized COVID-19 patients to aid clinical decision-making was considered to optimize COVID-19 health care (11–15). However, the long-term benefits of such treatment optimizers are rarely discussed (16). In this study, we are exploring the potential long-term cost savings and health benefits of the implementation of an AI system called Sandman.ICU designed for COVID-19 patients in the ICU.

The Sandman.ICU is currently implemented in several European ICUs as part of the European union project labelled ENVISION. The AI system developed during ENVISION collects data from various sources, such as ventilators and electrical impedance tomography. Moreover, it monitors COVID-19 patients in the ICU. The collected data will be processed in real-time using AI and aid clinical decision-making. For instance, the Sandman.ICU could provide an alarm when a patient is at increased risk for mortality. In addition, it will provide the clinician with an explanation of why this is the case, such as deteriorating oxygenation in combination with high blood pressure. This provides the clinician with the opportunity to optimize the treatment for this patient and potentially save their life.

When treatment is optimized because of the output of the Sandman.ICU, long-term health benefits, and costs savings might occur. Short-term benefits can be operationalized in several ways, for instance, reductions in ICU length of stay, duration of mechanical ventilation, hospitalization costs and mortalities. While the impact of reducing mortality rates on long-term costs and health benefits is relatively evident, the long-term benefits of reducing ICU length of stay or duration of mechanical ventilation are less apparent. However, it has been shown that the quality of life after discharge for ICU patients is heavily dependent on the duration of mechanical ventilation (17). According to Hodgson et al. (2017), each additional day of mechanical ventilation increases the odds of being moderately to severely disabled[1] after ICU discharge with 4% (OR: 1.04, CI: [1.01,1.08]). Hence, both reducing mortality rates as well as reducing mechanical ventilation duration will lead to health benefits in

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[1] Defined as having a WHODAS II score above 25%

the long-term. However, the differences in the quality of life, life years left and costs as a result of Sandman.ICU compared to care as usual are still to be determined. In this deliverable, these differences will be determined by means of a health-economic model. This model will demonstrate the economic and wider societal value of the Sandman.ICU. We will further elaborate on this model in the next sections.

2 Methods

2.1 Cost-effectiveness analysis

Health-economic models are commonly used as part of cost-effectiveness analyses to compare the effects of different health care interventions in the long term. Interventions are usually compared in terms of health consequences as well as financial consequences. By combining these two outcomes, one can make informed health care decisions on the possible advantages of different interventions. Since financial resources are limited, such analyses are useful to prioritize health care spending and maximize the benefits for patients. Using models that simulate disease-specific stages experienced by patients, novel interventions are compared to the current standard of care in cost-effectiveness analyses. These stages are valued health-wise as well as cost-wise. By simulating patients to move through the health stages, they accrue costs and life years corrected for quality of life in each of the stages. The average costs and QALYs resulting from the simulation then inform the cost-effectiveness outcome.

2.2 The model

To determine the potential health benefits and cost savings of the Sandman.ICU, a highly interpretable health-economic model was developed to simulate a population of 1000 patients with the German situation taken as a base case. All patients in the model have COVID-19 and during their hospitalisation, they all go to the general ward and the ICU. Moreover, we assumed that all patients are mechanically ventilated at a certain point during their hospitalization. As for the time horizon, we used the expected lifetime of the patients. The model consisted of four different stages, the hospitalization stage, the recovery stage, the healthy stage, and the mortality stage. All patients start in the hospitalization stage and can then move either to the recovery stage or to the mortality stage. The hospitalization stage has three substages, namely the general ward, the ICU, and the ICU with mechanical ventilation. All patients remain in each of these three substages for the mean length of stay. Next, patients in the recovery stage can go to the healthy stage or to the mortality stage. The recovery stage takes a maximum of 6 months, that is starting from discharge until 180 days after hospital admission. The recovery stage consists of two substages, namely, not to mildly disabled or moderate to severely disabled. Patients are in either of these two substages. The moderately to severely disabled substage could be viewed as post-intensive care syndrome (17), referred to as post-COVID syndrome for COVID-19 patients (18). The probability of being moderately to severely disabled is dependent on the duration of mechanical ventilation. A percentage of patients moves from the recovery stage to the mortality stage and the timing of this transition differs per person. Next, all surviving patients move to the healthy stage. From the healthy stage, patients move to the mortality stage after their expected lifetime. The mortality stage is an absorbing stage. The model was implemented in R version 4.2.1 (19). An overview of the health economic model can be found in Figure 1.

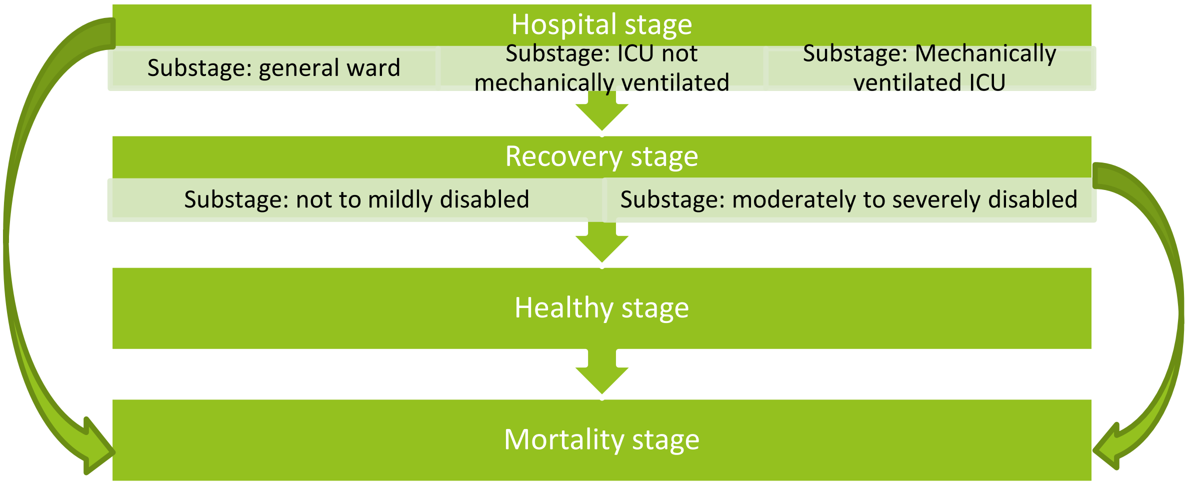

Figure 1. Overview of the health economical model.

2.3 Outcomes

Four different outcomes were used to assess the cost-effectiveness of the Sandman.ICU compared to care as usual. First, we assessed the incremental costs. Second, we assessed the incremental quality-adjusted life years (QALYs). QALYs are a combination of the life years gained and the quality of these life years (20). They are obtained by multiplying the life years left with a utility measuring the quality of these life years. In general, a utility of 1 refers to perfect health and a utility of 0 refers to a health state equivalent to death (20). Hence, when a person has 20 years left of life in full health, this is equivalent to $20 * 1 = 20$ QALYs. Next, the incremental cost-effectiveness ratio was used (ICER). The ICER is one of the most common metrics used in cost-effectiveness analysis and is calculated by dividing the increment in the price by the increment in the QALYs (21). Hence:

$$ICER = \frac{\text{Costs treatment} - \text{Costs care as usual}}{\text{QALYs treatment} - \text{QALYs care as usual}}$$

The ICER shows the additional costs for one additional QALY. This is subsequently compared to the amount a health institute 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 QALYs, to costs using the WTP and compares this to the incremental costs of the treatment (22). The incremental NMB is calculated by taking the incremental QALYs multiplied by the willingness-to-pay threshold (WTP) and subtracting the incremental costs, that is:

$$incremental\ NMB = (\text{QALYs treatment} - \text{QALYs care as usual}) * \text{WTP} - (\text{Costs treatment} - \text{Costs care as usual}).$$

Whenever the NMB is positive, an intervention is considered cost-effective. We used a WTP of €30,000 per QALY. However, since there is no official WTP per QALY in Germany (23), we also explored other values of the WTP, such as €50,000 and €80,000 per QALY.

2.4 Parameters

The parameters used in the health economic model can be found in Table 1. The majority of the parameters were obtained from the literature. At the start of the model, patients were assumed to be 66 years old. This average age was estimated from a frequency table of different age categories of 137,750 German ICU COVID-19 patients (24). Moreover, this same study showed that 37.49% of the patients were female (24). Hence, this percentage was used to represent the number of females and males in the model. Moreover, in accordance with the literature, an in-hospital mortality of 33.36% was used (24). Patients remained in each of the hospitalization substages for the mean LOS. The mean LOS and standard deviations of LOS were acquired using an administrative data set of 386 mechanically ventilated COVID-19 patients admitted to the University Hospital Frankfurt am Main between February 1, 2020, and July 1, 2021. Elaborate information on these data can be found in Zwerwer et al. (under review, see Appendix) (25). We conservatively assumed that, on average, the Sandman.ICU reduced the duration of mechanical ventilation by half a day and the mortality rates by 1%; both these parameters were estimated using expert opinion. Next, of all patients discharged from the hospital alive, 24.81% were moderately to severely disabled, which was the base rate in the study of Hodgson et al. (2017) (17). We assumed that this percentage of moderately to severely disabled people was applicable for the mean duration of mechanical ventilation in the study of Hodgson et al. (2017), which was equal to an estimated 4.6 days. Moreover, according to this study, each day of mechanical ventilation leads to an increase of 4% in the odds of being moderately to severely disabled (17). Hence, in our model, each additional day of mechanical ventilation above 4.6 days led to an increase in the odds of being moderately to severely disabled by 4% and each day of mechanical ventilation below 4.6 days decreased the odds of being moderately to severely disabled by 4%. A total of 6.2% of the patients deceased in the recovery stage (26). This is in accordance with the study of Günster et al. (2021), who showed in a German study that from the 6,518 COVID-19 patients discharged alive from the hospital, 405 patients died within six months after their initial hospital admission. Moreover, we assumed that the timing of the deaths in the recovery stage followed a gamma distribution with a mean mortality time of approximately 16 days (27). This distribution was bounded from above by 180 days after the hospital admission, that is, 180 days after discharge minus the full LOS in the hospital. Hence, when the mortality was after 180 days after hospital admission, the day of the mortality was adjusted to 180 days minus the mean of the full hospital LOS. Next, all surviving patients were assumed to be fully recovered six months after hospital admission and resumed their life as usual until they reach the age of their life expectancy (corrected for sex). These life years were discounted with a 3% discount rate (28).

2.4.1 Costs

The costs estimated for the Sandman.ICU are based on a clinic with 20-40 beds and 20-30 users (clinical staff). Costs are based on internal communication at Löwenstein medical. Costs for set up and installation were estimated at € 25,000 – € 30,000. Training for the system costs approximately € 5,000 – € 6,000. Finally, hardware, service and remote support and licensing costs, respectively, € 500, € 600 and € 800 per bed site per year. We assumed that the system would last ten years. Moreover, we assumed that the Sandman.ICU will only be used for COVID-19 patients during the mechanically ventilated days. The total price per mechanically ventilated bed day of the Sandman.ICU in the health-economic model depends on the German mechanically ventilated COVID-19 ICU occupancy. The mechanically ventilated COVID-19 ICU occupancy was based on the average COVID-19 ICU occupancy in Germany for 2022. This is reported weekly by the European Centre for Disease Prevention and Control (29). The average German COVID-19 ICU occupancy in 2022 was 1518.75 beds. This number was subsequently divided by the most recent number of ICU beds available in Germany published by the Statistisches Bundesamt in 2020, which is 27,604 ICU beds (30). Finally, the result of this ratio was multiplied by 75.7%, which is the percentage of mechanically ventilated patients in Germany (25). This led to an approximated mechanically ventilated COVID-19 ICU occupancy of 4.2% per year. Next, assuming an ICU ward with 20 beds and 20 users, we estimated the price of the Sandman.ICU per bed per year in the following way:

$$\begin{aligned}
&Price\ per\ bed\ per\ year \\
&\quad = \frac{Set\ up\ and\ installation\ \ + Training}{number\ of\ beds * nunber\ of\ years\ system\ lasts} + hardware \\
&\quad + service\ and\ remote\ support + licensing \\
&\quad = \frac{25{,}000 + 5{,}000}{20 * 10} + (500 + 600 + 800) \\
&\quad = € \ 2{,}050
\end{aligned}$$

Next, the costs per mechanically ventilated bed day can be obtained by dividing through the mechanically ventilated COVID-19 ICU occupancy and finally through the number of days per year.

Hence:

$$
\begin{aligned}
&\mathit{Price\ per\ mechancically\ ventilated\ bed\ day}\\
&\qquad = \frac{\mathit{Price\ per\ bed\ per\ year}}{\frac{\mathit{Mechanically\ ventilated\ COVID-19\ ICU\ occupancy}}{\mathit{Number\ of\ days\ in\ a\ year}}}\\
&\qquad = \frac{2050}{\frac{0.042}{365}}\\
&\qquad = € \, 133.72
\end{aligned}
$$

Converting these costs to purchasing power parities (ppp) 2021 euros (31) leads to a final price of €120.41 per mechanically ventilated bed day.

Costs for each hospital substage were acquired from a study by Zwerwer et al. (under review, see Appendix) (25), which estimated the daily costs for each hospital substage with generalized linear models using administrative costing data with 510 ICU COVID-19 patients of the University hospital Frankfurt am Main. Only costs for an additional day in each sub-stage were considered, that is, disregarding the effect of age, gender, and comorbidities on the costs. The costs were converted to 2021 PPP euros. Costs for the recovery stage were estimated from a Singaporean study (32). In this study, rehabilitation costs were evaluated for twenty-seven 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 € 1969.47 (inflated to 2021 (33), converted to PPP euros (34)). 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. Assuming that from all patients discharged from the hospital alive, 24.81% were moderately to severely disabled (17), rehabilitation costs for not to mildly disabled patients could be estimated in the following way:

$$
\mathit{rehabilitation\ costs\ not\ to\ mildly\ disabled\ patients} = \frac{1{,}969.47}{1.5} = € \, 1{,}312.98
$$

Rehabilitation costs for moderately to severely disabled patients were obtained by multiplying the afore mentioned amount by three. Finally, we assumed that the simulated patients had no further medical costs related to their COVID-19 hospital admission during the healthy stage. No discounting was applied to the costs since we assumed patients only incur costs during the first year of the model.

2.4.2 Utilities

The calculation of the health benefits required the quality of life in each of the (sub) stages of the model, referred to as utilities. The utilities for the hospitalization substages were calculated using disutilities. These disutilities were subtracted from the utilities in the healthy stage, which is discussed further on. The disutilities of the different hospitalization substages were obtained from a study by the Institute for Clinical and Economic Review (2020) on the cost-effectiveness of treating hospitalized COVID-19 patients with Remdesivir (35). Utilities in the recovery stage 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 (17). Moreover, utilities in the healthy stage were taken from Szende et al. (2014). These utilities were obtained using the time trade-off method, which is a method to value different health states. They distinguished different utilities for German males and females of different age groups. Hence, we used the percentage of females and the age of the patients mentioned before to determine the utility for each patient. Moreover, the utilities were adjusted accordingly when the patients aged over time. The obtained utilities were multiplied by the life years in the healthy stage to calculate the QALYs for patients in this stage.

Table 1. Parameters of the health-economic model

Group of parameters	**Parameter**	**Base case (i.e. mean)**	**Standard deviation**	**One-way sensitivity analysis boundaries**	**Distribution probabilistic sensitivity analysis**	**Source**	**Studied population in source**
Population parameters	Mechanically ventilated ICU bed occupancy[1]	4.2%	NA	NA	NA	European Centre for Disease Prevention and Control, 2022 (29) and Statisches Bundesamt, 2020 (30) and Zwerwer et al. (under review, see Appendix) (25)	German COVID-19 ICU patients
	Age[2]	66	NA	NA	NA	Kloka, Blum, Old, Zacharoswki and Friedrichson, 2022 (24)	German ICU covid-19 patients
	Female	37.49%	NA	NA	NA	Kloka, Blum, Old, Zacharoswki and Friedrichson, 2022 (24)	German ICU covid-19 patients
In-hospital parameters	Length of stay general ward	4.15	7.74	95% ci: 3.38-4.92	Gamma	Administrative costing data from the University hospital Frankfurt am Main	German mechanically ventilated COVID-19 patients

	Length of stay ICU not mechanically ventilated	5.31	6.72	95% ci 4.63 – 5.98	Gamma	Administrative costing data from the University hospital Frankfurt am Main	German mechanically ventilated COVID-19 patients
	Duration of mechanical ventilation	11.13	14.87	95%ci: 9.64 -12.62	Gamma	Administrative costing data from the University hospital Frankfurt am Main	German mechanically ventilated COVID-19 patients
	In-hospital mortality	33.36%	0.001	Base case +- 0,10*base case: 30.02- 36.70	Beta	Kloka, Blum, Old, Zacharoswki and Friedrichson, 2022 (24)	German ICU COVID-19 patients
Recovery stage	Duration of mechanical ventilation for non-disabled or mildly disabled patients post discharge[3,4,5A]	4.18	3.62	Base case +- 0,10*base case: 3.76- 4.60	Gamma	Hodgson et al. (2017) (17)	Australian mechanically ventilated ICU patients
	Duration of mechanical ventilation for moderately to severely	6.06	6.14	Base case +- 0,10*base case: 5.45-6.67	Gamma	Hodgson et al. (2017) (17)	Australian mechanically ventilated ICU patients

	disabled patients post discharge[3,4,5A]						
	Probability of being moderately to severely disabled post discharge[4]	24.81%	0.03	95% ci: 19.79 – 30.58	Beta	Hodgson et al. (2017) (17)	Australian mechanically ventilated ICU patients
	Odds ratio of days of mechanical ventilation for being moderately to severely disabled post discharge	1.04	0.33	95% ci: 1.01-1.08	Lognormal	Hodgson et al. (2017) (17)	Australian mechanically ventilated ICU patients
	Six months mortality	6.21%	0.003	95% ci: 5.65-6.83	Beta	Günster et al. (2021) (26)	German hospitalized COVID-19 patients
	Time to post-discharge mortality[3]	15.63	4.44	Base case +-0,10*base case: 14.07 – 17.19	Gamma	Moestrup et al. (2022) (27)	Danish ICU COVID-19 patients
Life expectancy	Life expectancy for a female of age 66	20.09	NA	NA	NA	Federal Statistics Office (2022) (36)	General German population

	Life expectancy male of age 66	16.83	NA	NA	NA	Federal Statistics Office (2022) (36)	General German population
Utilities	General ward disutility[5B,6]	0.49	10% * base case: 0.05	Base case +- 0,10*base case: 0.44 – 0.54	Beta	Institute for clinical and economic review (2020) (35)	Patients with influenza or *Clostridium difficile* infection
	ICU not mechanically ventilated disutility[5B,6]	0.69	10%* base case: 0.07	Base case +- 0,10*base case: 0.62 – 0.76	Beta	Institute for clinical and economic review (2020) (35)	Patients with influenza or *Clostridium difficile* infection
	Mechanical ventilation disutility[5B,6]	0.79	10%*base case: 0.08	Base case +- 0,10*base case: 0.71 – 0.87	Beta	Institute for clinical and economic review (2020) (35)	Patients with influenza or *Clostridium difficile* infection
	Recovery stage; not disabled to mildly disabled[5C]	0.77	0.26	95% ci: 0.73- 0.81	Beta	Hodgson et al., 2017 (17)	Australian mechanically ventilated ICU patients
	Recovery stage; moderately to severely disabled[5C]	0.5	0.26	95% ci: 0.44– 0.56	Beta	Hodgson et al., 2017 (17)	Australian mechanically ventilated ICU patients

	Healthy stage; 65-74 female[5D]	0.874	0.18	95% ci: 0.85 - 0.90	Beta	Szende et al., 2014 (37)	German general female population
	Healthy stage; 75+ female[5D]	0.820	0.21	95% ci: 0.79 - 0.85	Beta	Szende et al., 2014 (37)	German general female population
	Healthy stage; 65-74 male[5D]	0.915	0.16	95% ci: 0.89 - 0.94	Beta	Szende et al., 2014 (37)	German general male population
	Healthy stage; 75+ male[5D]	0.880	0.16	95% ci: 0.85 – 0.91	Beta	Szende et al., 2014 (37)	German general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	120.41	NA	NA	NA	See section 2.2, Eurostat (2021) (31)	NA
	General ward per day[5E]	372.97	450.83	95% ci: 333.74–412.19	Gamma	Zwerwer et al. (under review, See Appendix) (25), Eurostat (2021) (31)	German ICU COVID-19 patients
	ICU not mechanically ventilated per day[5E]	835.12	925.65	95%ci: 754.59 - 915.65	Gamma	Zwerwer et al. (under review, see Appendix) (25), Eurostat (2021) (31)	German ICU COVID-19 patients

	Mechanically ventilated per day[5E]	2,003.35	1,428.32	95%ci: 1,879.09 – 2,127.61	Gamma	Zwerwer et al. (under review, see Appendix) (25), Eurostat (2021) (31)	German ICU COVID-19 patients
	Recovery stage; not disabled to mildly disabled per month[7]	1,312.98	10%*base case: 131.30	Base case +- 0,10*base case: 1,181.68 – 1,444.28	Gamma	Assumption & Ong, Tay & Tham (2021) (32)	Assumption & Singaporean mechanically ventilated COVID-19 survivors
	Recovery stage; moderately disabled to severely disabled per month[7]	3,938.94	10%* base case: 393.89	Base case +- 0,10*base case: 3,545.05 – 4,332.83	Gamma	Assumption & Ong, Tay & Tham (2021) (9)	Assumption & Singaporean mechanically ventilated COVID-19 survivors
	Intervention effect on mortality	1%	0.1%	Base case +- 0,10*base case: 0.9%-1.1%	Beta	Assumption based on expert opinion	Assumption based on expert opinion
	Intervention effect on the duration of mechanical ventilation	0.5	0.05	Base case +- 0,10*base case: 0.45-0.55	Gamma	Assumption based on expert opinion	Assumption based on expert opinion

1. The mechanically ventilated ICU bed occupancy was estimated by multiplying the ICU bed occupancy with the proportion of mechanically ventilated patients. The ICU occupancy was obtained by taking the average COVID-19 ICU occupancy in 2022 (29) and dividing this by the most recent number of ICU beds available in Germany (30). The proportion of mechanically ventilated patients was obtained from Zwerwer et al. (under review, see Appendix).
2. Estimated from Table 2 of Kloka, Blum, Old, Zacharoswki and Friedrichson, 2022 (24).
3. Estimated using the method of moments.
4. The combination of the duration of mechanical ventilation for non-disabled or mildly disabled patients together with the duration of mechanical ventilation for moderately to severely disabled patients and the probability of being moderately to severely disabled were used to estimate the mean duration of mechanical ventilation for all patients in (17), this was assumed to be the duration for which the base case probability of being moderately to severely disabled -post-ICU hold.
5. In the probabilistic sensitivity analysis ratios were kept fixed between these variables (grouped with letters).
6. Utilities in different hospitalization states were calculated by taking the utility for the general population of females and males of age 66, taking into account the ratio of males to females, and subtracting the disutilities for each stage.
7. Rehabilitation costs for the full discharged patient population were taken from (32), prices adjusted to PPP 2021 euro's using harmonised indices of consumer prices and purchasing power parities from Eurostat (31,38). Costs for not-disabled to mildly disabled patients and moderately to severely disabled patients were estimated using the proportion of moderately to severely disabled patients and using the assumption that costs for moderately to severely disabled patients were three times as high compared to not to mildly disabled patients.

2.5 Base case analysis and one-way sensitivity analysis

All outcomes discussed in Section 2.3 were evaluated for the base case scenario. This analysis was performed for patients of age 60, 66 and 70 years old. Next, a one-way sensitivity analysis was performed. In a one-way sensitivity analysis, one parameter of the model is varied until a prespecified boundary, and the effects of this on the outcomes are evaluated. 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 Table 1). The effects on the ICER are shown in a tornado plot, which illustrates the most influential parameters in the model.

2.6 Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed. Hence, each parameter was probabilistically varied according to a predefined distribution (see Table 1). In case standard deviations were not available, we used 10% of the base case value. For hospital LOS, hospitalisation costs and the timing of mortalities in the recovery stage, a gamma distribution was used. For probabilities and utilities, we used a Beta distribution. For the odds ratio of being moderately to severely disabled -post-discharge, a lognormal distribution was used. A thousand different parameter combinations were used, 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 plotted the different WTP thresholds against the mean incremental NMB. Subsequently, we ran the PSA for different treatment costs. The daily treatment costs ranged from €0 to €600 per mechanically ventilated bed in steps of €5. We plotted the mean incremental NMB for the different treatment costs using a WTP of €30,000, €50,000 and €80,000 per QALY. Finally, to explore the impact of different treatment effects, we ran the PSA with a thousand iterations for different intervention effects on mortality and different intervention effects on the duration of mechanical ventilation. The mortality intervention effect varied between 0 and 10% in steps of 0.3%, and the reduction in the duration of mechanical ventilation varied between 0 and 3 days of mechanical ventilation in steps of 0.1 days. This was performed for a treatment price of €120.41, which corresponds to a mechanically ventilated ICU occupancy of 4.2%. The mean incremental NMB was plotted in a heatmap for each of these scenarios, assuming a WTP of € 30,000.

2.7 Applying the health economical model to other European countries

Cost-effectiveness of the Sandman.ICU was also assessed in all other European countries in which the Sandman.ICU is implemented, that is England, Hungary, Italy, Lithuania, Portugal, Romania, Slovenia and Spain (see Figure 2). Model parameters were adjusted to the specific country whenever possible. In case no information on costs could be found, German costs were converted using purchasing power parities from Eurostat and the Organisation for Economic Co-operation and Development (OECD) (31,34). When parameters for a specific country where unavailable from the literature, parameters of neighbouring countries were used if available. Otherwise, parameters of the German base case were assumed. An overview of all parameters used per country can be found in Section 7 (the Appendix).

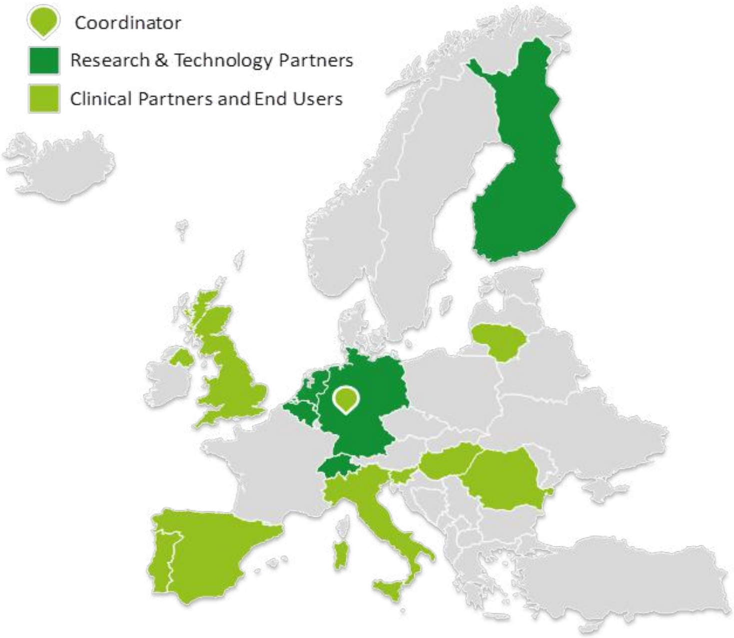

Figure 2. All countries participating in ENVISION. Germany and all light-green countries are countries in which the Sandman.ICU was implemented and for which a cost-effectiveness analysis was performed.

For all participating countries, a table was created showing the cost-effectiveness of the base case for different ages while assuming an intervention effect on the mortality of 1% and an intervention effect on the duration of mechanical ventilation of 0.5 days. Moreover, for each country, we performed a PSA. These results were shown in a cost-effectiveness plane and cost-effectiveness acceptability curve. Moreover, the mean incremental NMB was plotted against different WTP and the effect of different prices for the Sandman.ICU on the mean incremental NMB was explored. Finally, a heatmap was created showing the impact of different intervention effects on the cost effectiveness of the Sandman.ICU, while keeping the price of the Sandman.ICU fixed and a WTP of that specific country.

3 Results

3.1 Base case

The base case results of the model can be found in Table 2 for different ages. 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 0.5 days in mechanical ventilation and a WTP of € 30,000.

Table 2. Results of the base case

Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost-effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	29,598.24	9.91	NA	NA	NA	NA
60	Treatment	29,893.84	10.06	295.60	0.15	1,980.84	4,181.34
66	Care as usual	29,598.24	8.03	NA	NA	NA	NA
66	Treatment	29,893.84	8.15	295.60	0.12	2,442.62	3,334.96
70	Care as usual	29,598.24	6.62	NA	NA	NA	NA
70	Treatment	29,893.84	6.72	295.60	0.10	2,958.19	2,702.21

*Assuming a willingness to pay € 30,000

3.2 One-way sensitivity analysis

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 duration of mechanical ventilation and the daily costs of mechanical ventilation. The higher the mean duration of mechanical ventilation, the higher the ICER. Moreover, lowering the intervention effects and the costs of mechanical ventilation leads to a higher ICER. The Tornado plot showing the effect of varying the different parameters on the ICER can be found in Figure 3.

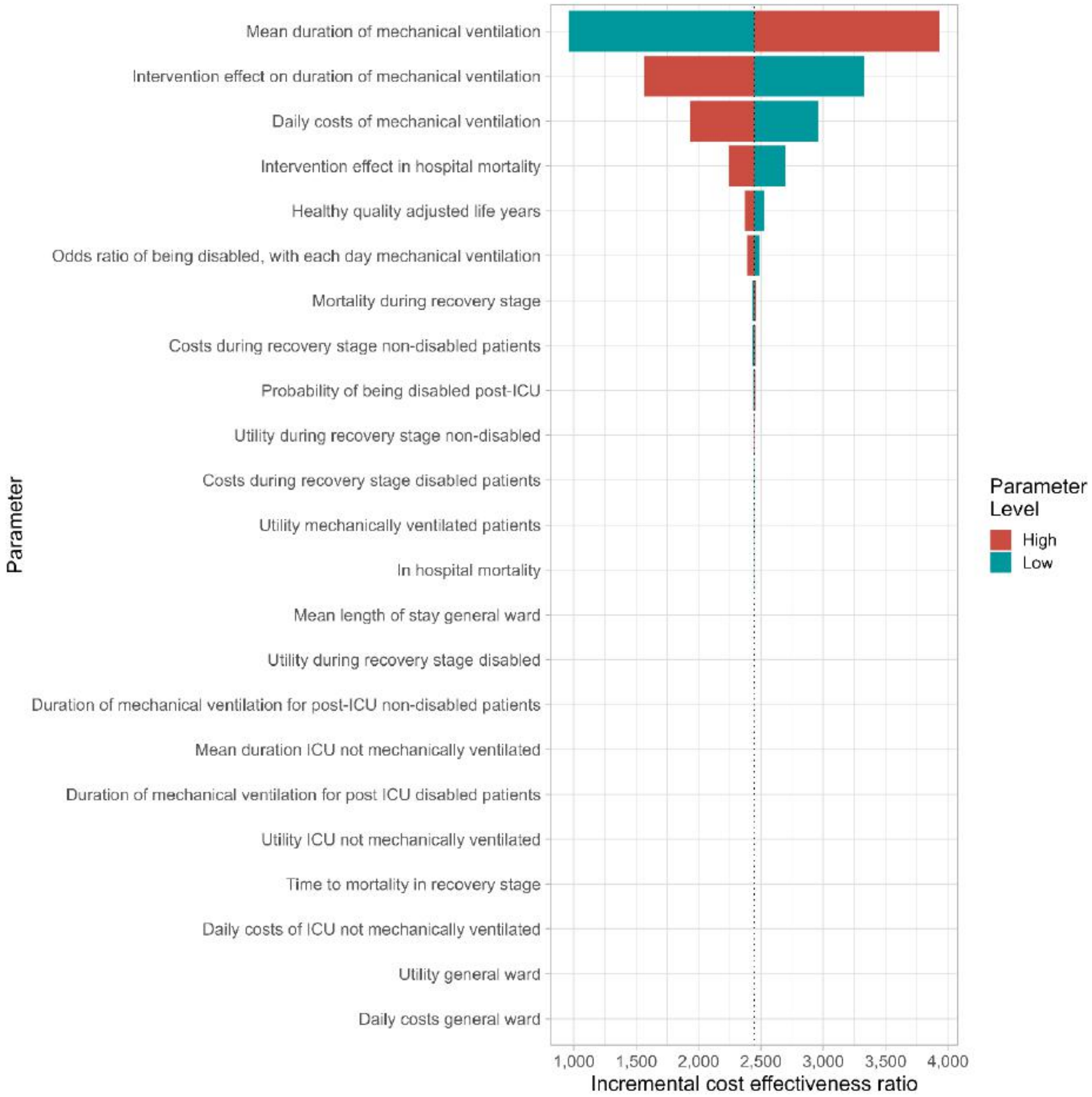

Figure 3. Tornado plot showing the effects of varying the different parameters on the ICER

3.3 Probabilistic sensitivity analysis

The mean results of the PSA show that with an intervention effect on the mortality of 1%, a reduction of half a day mechanical ventilation, a Sandman.ICU price per mechanically ventilated bed day of €120.41 and a WTP of € 30,000 for the usage of the Sandman.ICU for mechanically ventilated COVID-19 patients is cost-effective with an incremental NMB of € 3,277.42. Under the aforementioned parameter settings, the Sandman.ICU leads to an additional 0.12 QALY per person on average while paying an additional € 342.57. All the simulated scenarios in the PSA showed health benefits, that is, increased QALYs, and 55.6% of the simulated strategies in the PSA were costs saving. The results of the PSA are visualized in the cost-effectiveness plane in Figure 4. All scenarios are in either the northeast or southeast quadrant.

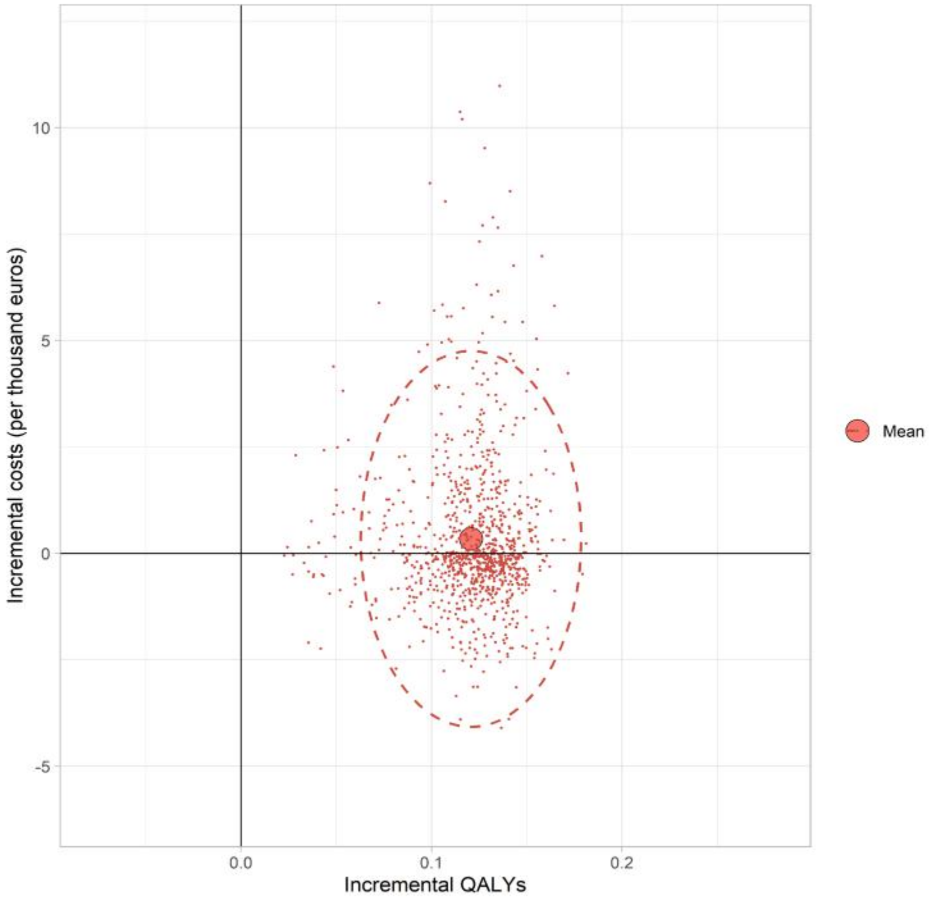

Figure 4. Cost-effectiveness plane for the Sandman.ICU compared to the current standard-of-care. Visualized with the 95% confidence ellipse and the mean of all iterations. All iterations of the PSA are either in the southeast or northeast quadrant.

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 visualized using a ceac (Figure 5). Whenever the WTP is € 0.00, there is a probability of 55.6% that the treatment is cost-effective. Overall, for WTP of € 10,000 and above, there is a high probability (≥ 78.9%) that the Sandman.ICU is cost-effective. This probability increases for higher WTP and exceeds 95% for WTP of € 40,000 and above.

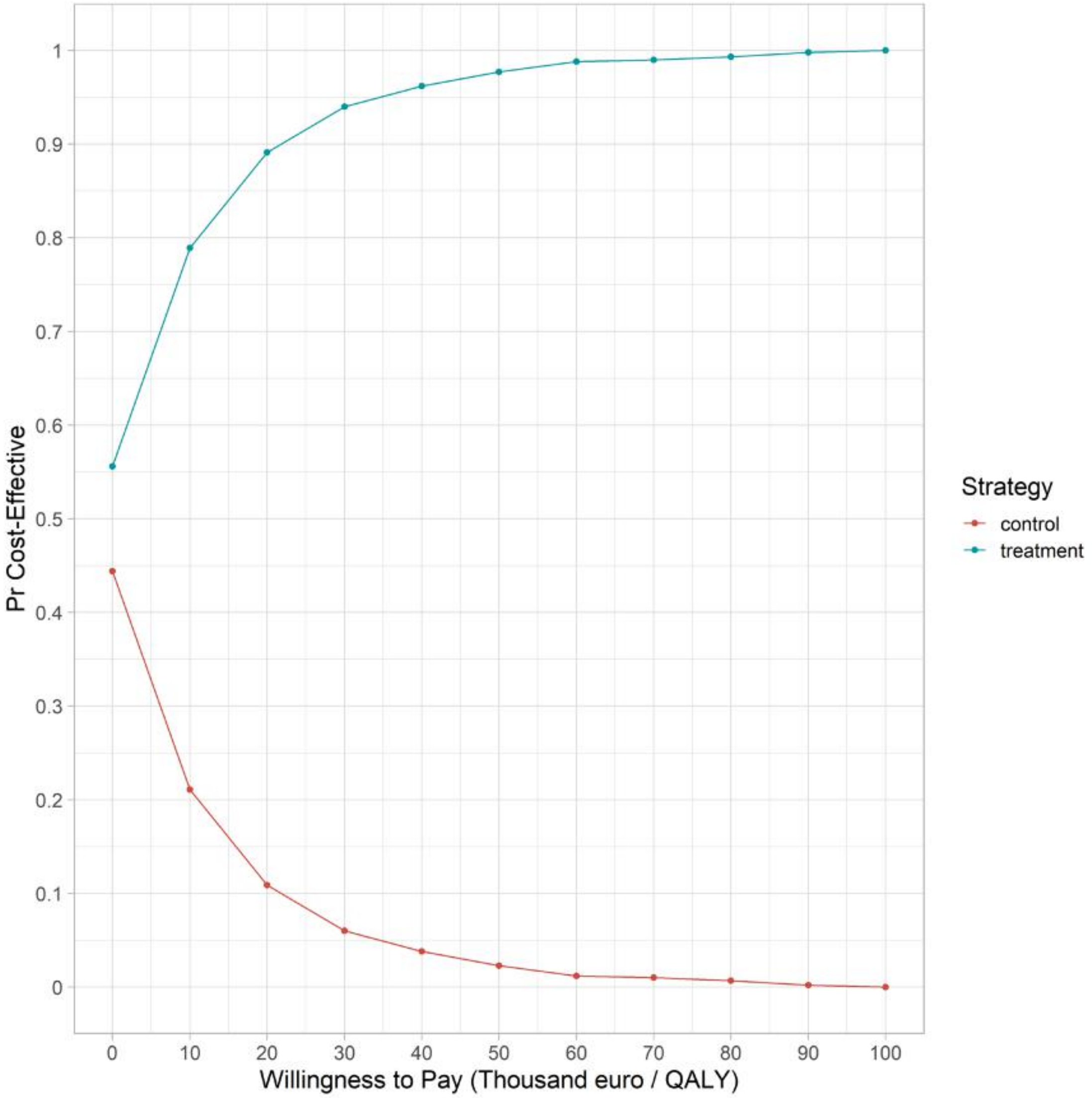

Figure 5. Cost-effectiveness acceptability curve showing the probability that the Sandman.ICU is cost-effective versus care as usual.

Relatedly, the WTP can be plotted against the mean incremental NMB of the PSA (see Figure 6). Note that for WTP ranging from € 10,000 to € 100,000, the mean NMB remains positive. This confirms that under the assumptions discussed before the Sandman.ICU will be cost-effective.

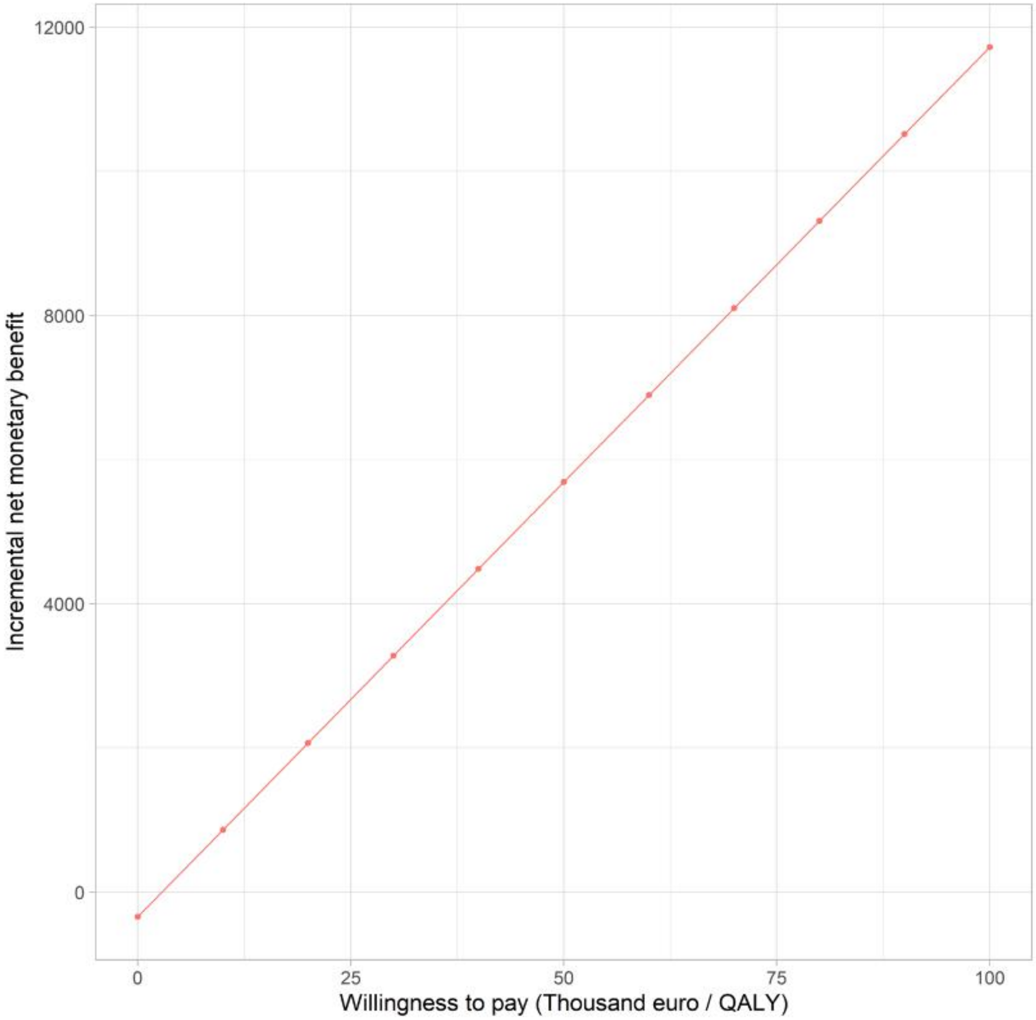

Figure 6. Willingness to pay against the mean net monetary benefit of the probabilistic sensitivity analysis. The incremental net monetary benefit is positive for a willingness to pay between € 10,000 and € 100,000.

Next, the price of the treatment of the Sandman.ICU was varied. The mean results of the PSA for different prices and different WTP can be found in Figure 7. Moreover, the second x-axis shows the mechanically ventilated COVID-19 ICU occupancy, which determines the daily price of the Sandman.ICU (see Section 2.4.1 Costs). The plot shows that assuming a WTP of € 30,000 below an occupancy of approximately 1.15%, that is a daily price of € 440.49 per mechanically ventilated bed, the Sandman.ICU can no longer be considered cost-effective.

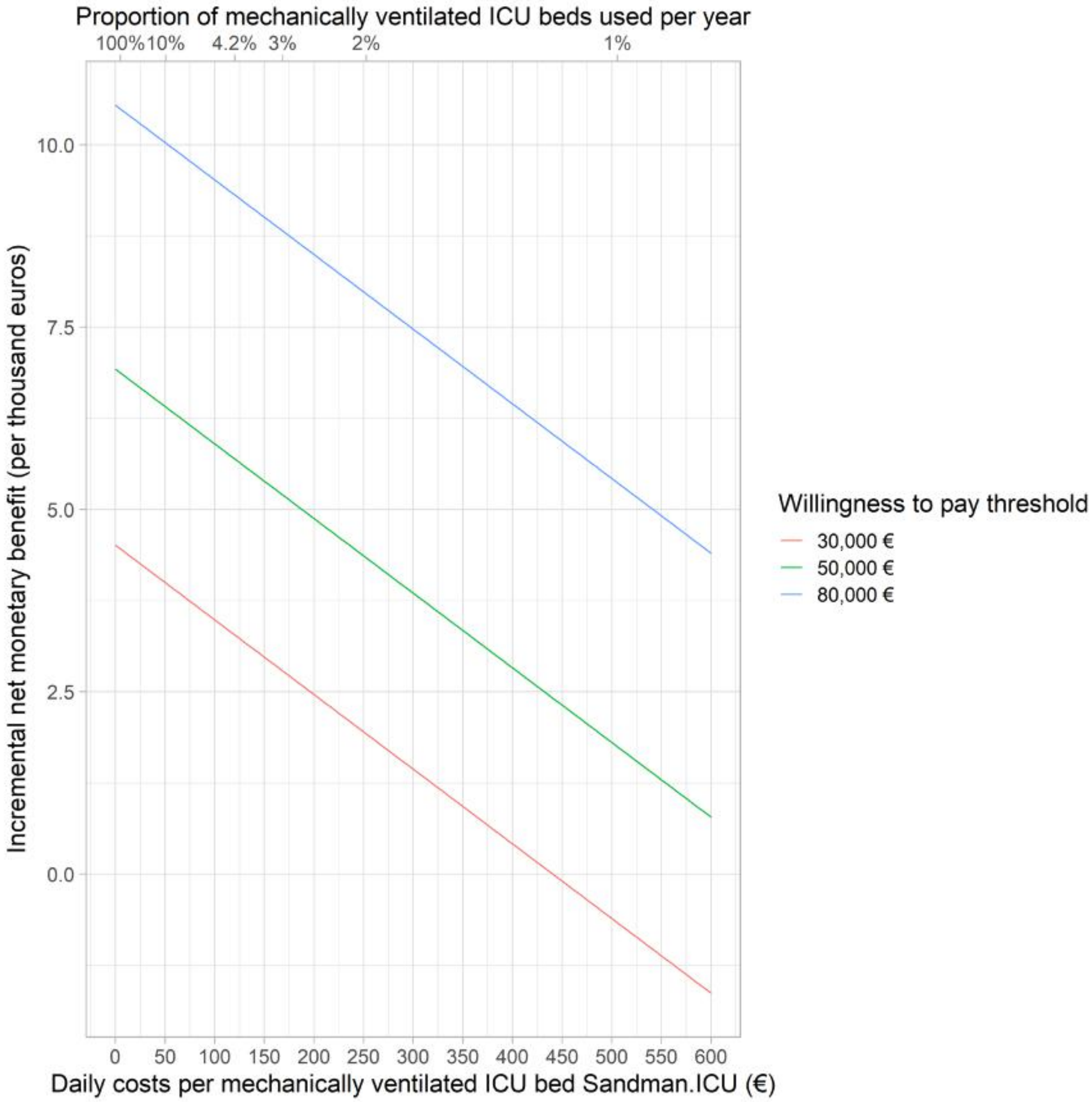

Figure 7. Incremental net monetary benefit for the Sandman.ICU for different prices and ICU occupancy. The different lines represent different WTP thresholds ranging from € 30,000 to € 80,000

Finally, the impact of different intervention effects on the incremental NMB was explored. Keeping the daily price per mechanically ventilated bed at € 120.41 and a WTP of € 30,000 a PSA was performed for different intervention effects ranging from a reduction in mortality of 0 to 10% and a reduction in the duration of mechanical ventilation ranging from 0 to 3 days. The heatmap showing the mean incremental NMB resulting from this analysis can be found in Figure 8. Interestingly, the incremental NMB is positive for the majority of the plot. Hence, the Sandman.ICU appears to be cost-effective for a wide range of intervention effects. However, for small 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 0.6

days in the mechanical ventilation duration, or a reduction in mortality of 0.3% and no reduction in the days of mechanical ventilation the treatment is not considered cost-effective.

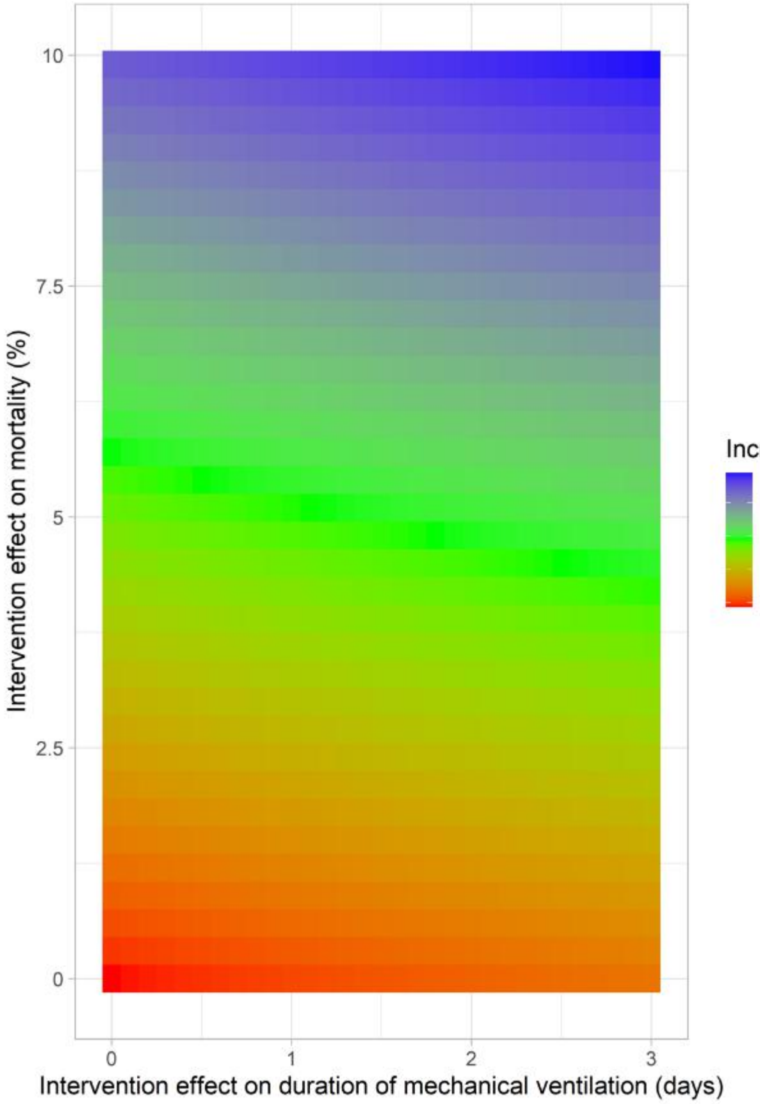

Figure 8. Incremental net monetary benefit for different intervention effects on mortality and duration of mechanical ventilation. Assuming a treatment price of € 120.41 per mechanically ventilated bed day and a WTP of € 30,000 per QALY.

3.4 Results of cost-effectiveness analysis of the Sandman.ICU in other European countries

The results of the cost-effectiveness analysis for England, Italy, Hungary, Lithuania, Portugal, Romania, Slovenia and Spain can be found in the Appendix (Section 7). Results show that under the aforementioned assumptions, the Sandman.ICU will be cost-effective in the base case for all countries involved in ENVISION. In all scenarios, the Sandman.ICU provided health benefits. Furthermore, results showed that the Sandman.ICU provided cost savings in the base case scenarios of Hungary, Lithuania, Portugal, Romania and Spain. In England, Italy and Slovenia, the costs for the treatment with the Sandman.ICU are only slightly higher (< € 700 per patient) compared to the costs for care as usual. Finally, the PSA showed that the Sandman.ICU will be cost-effective under a wide set of scenarios for all countries involved in ENVISION.

4 Discussion

A health-economic model was developed to explore the cost-effectiveness of the Sandman.ICU. The Sandman.ICU is an AI system developed during the ENVISION project aiming to aid clinicians in clinical decision-making in the treatment of critically ill COVID-19 patients. Following the recommendations of the Sandman.ICU could potentially improve patient care. However, the extent to which patient care improves is currently unknown. Therefore, we assumed that the usage of the Sandman.ICU improves the treatment of COVID-19 patients in the ICU in two different ways, namely by reducing mortalities and reducing the duration of mechanical ventilation. Based on the assumed intervention effects, long-term health benefits and costs were calculated using the health-economic model. This model showed that under the base-case scenario, the treatment with the Sandman.ICU was cost-effective while assuming a WTP of € 30,000. Next, both a one-way sensitivity analysis as well as a PSA were performed. The cost-effectiveness of the Sandman.ICU was explored under a broad range of scenarios. In most of these scenarios, the Sandman.ICU was cost-effective. In case of very low intervention effects or very low mechanically ventilated COVID-19 ICU occupancy the Sandman.ICU is no longer considered cost-effective.

In the one-way sensitivity analysis, the importance of the mean duration of mechanical ventilation in the health-economic model on the ICER was quite remarkable. One would expect the intervention effects to be the most important as this is what essentially changes between care as usual and the treatment. Further exploration of the model showed that the importance of the duration of mechanical ventilation is indirectly related to the price of the treatment with the Sandman.ICU. Hence, since treating a patient with the Sandman.ICU costs an additional € 120.41 per mechanically ventilated bed day, the total treatment costs increase. Therefore, a longer duration of mechanical ventilation increases the ICER. Importantly, the model did not take into account the effect of a longer duration of mechanical ventilation on the mechanically ventilated COVID-19 ICU occupancy, which should consequently increase and therefore lower the costs of the Sandman.ICU per mechanically ventilated bed day. However, these costs were not adjusted as the future mechanically ventilated COVID-19 ICU occupancy is relatively hard to estimate considering the uncertainty in the COVID-19 situation and the emergence of new mutations. Therefore, the effect of different mechanically ventilated COVID-19 ICU occupancies on the cost-effectiveness of the Sandman.ICU was thoroughly explored. Under most scenarios (occupancy ranging between 100% and 1.15%) the Sandman.ICU seemed cost-effective. However, in case of extremely low occupancy, this is no longer the case.

While the proposed health-economic model provides an opportunity to explore the cost-effectiveness of the Sandman.ICU, the model does have some limitations. Firstly, the basic structure of the model might oversimplify reality. For instance, in the model, it is assumed that in the recovery stage, the utilities for the quality of life remain stable at the reported utility scores of Hodgson et al. (2017)(17). However, this is not 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) (17). Hence, utilities in the recovery stage have 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 stage on the ICER was negligible in the tornado plot. Next, the utilities, the odds ratio and probability used for disability in the recovery stage were not specific for COVID-19 patients. However, an increased risk for lower functional status at six months post-discharge with each day of mechanical ventilation has also been found for COVID-19 patients (39). The extent to which this lowers the functional status was, however not reported in this study. Additionally, the estimated rehabilitation costs came from a Singaporean study (32). While we adjusted these costs to German costs using purchasing power parities, rehabilitation costs in Germany might be different. However, as far as we were aware, this Singaporean study is the only study estimating rehabilitation costs for COVID-19 discharged patients. Therefore, these costs were used as a proxy for the German rehabilitation costs. Importantly, the effect of the rehabilitation costs on the ICER was negligible. Hence, we do not expect this to have a big impact on the results of the health-economic model. Furthermore, the six months post-discharge mortality assumed in our model came from a general German COVID-19 hospital population (26). While no studies have explored the difference between six months mortality of general hospitalized COVID-19 patients and mechanically ventilated COVID-19 patients yet, one would expect a higher six-month mortality rate for the discharged mechanically ventilated COVID-19 patients. Furthermore, in the health-economic model, it was assumed that all patients fully recovered six months after hospital admission. Post-COVID-19 ICU recovery differs per patient and takes, in general, longer than six months. For instance, in a Chinese study, researchers found that at six months after symptom onset, 86% of the critically ill patients still experienced post-COVID-19-like symptoms, with fatigue and muscle weakness mentioned as the most common ones (81%) (40). Moreover, at six months after symptom onset respectively, 41% and 32% of critically ill patients experienced pain or discomfort and anxiety or depression. Moreover, in a Dutch multicentre cohort study of 11 ICUs, almost 75% of the surviving patients reported physical symptoms one year after ICU admission (41). 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 a life expectancy for the general population was assumed, while in reality ICU survivors are at increased risk of mortality until 15 years after discharge (42). Nevertheless, the highest excess mortality is within the first year after discharge (42). Moreover, the effect of mortality in the recovery stage on the ICER was negligible in the tornado plot. Therefore, we do not expect the results of this study to be much affected by this. Finally, while we strived to attain all parameters specifically for the country, the cost-effectiveness was assessed for, in some cases, this was not possible, and therefore proxies were used from other countries. Similarly, some parameters used in the model, for instance, age and percentage of females, were from slightly different populations. This might affect the precision of the cost-effectiveness analysis performed. Relatedly, changes in the COVID-19 immunity over time and different mutations might influence the parameters in the model and therefore affect the cost effectiveness analysis performed. Finally, in the model, all patients get mechanically ventilated, while the Sandman.ICU might also provide benefits for non-mechanically ventilated patients. In an alternative model for non-mechanically ventilated patients, assumptions can be made regarding reductions of the ICU LOS. It has been shown that each day spent extra in the ICU leads to 4.4% higher odds of having a decreased quality of life six months after discharge (39). Therefore, a similar model could be used in this situation too.

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 (43). 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 much flexibility and can therefore, easily be adjusted to the situation in other countries, different treatment options and other diseases. Moreover, when the final intervention effects of the Sandman.ICU are known the cost-effectiveness results can easily be found in the heatmap of incremental NMB (see Figure 8). Therefore, when the Sandman.ICU models are running in real-time the true cost-effectiveness can be examined directly.

5 Conclusion

While the exact impact of the Sandman.ICU on the healthcare of COVID-19 patients is not yet determined; we strived to estimate its cost effectiveness regardless of the exact intervention effect. Our initial results showed that under a wide set of scenarios the Sandman.ICU can potentially be cost-effective and provide health benefits for, on average a slightly higher price. However, these results need to be interpreted with caution until more is known about the direct effects of the Sandman.ICU.

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7 Appendix

7.1 England

7.1.1 Parameters

Group of parameters	Parameter	Base case (i.e. mean)	Standard deviation	Distribution probabilistic sensitivity analysis	Source	Studied population in source
Country specific parameters	Willingness to pay	29,385.96	NA	NA	McCabe Claxton & Culyer (2008) (44) OECD (2021) (34), Eurostat (2021) (31)	NA
	Mechanical ventilated ICU occupancy[1]	4.3%	NA	NA	National Health Institute England (2022) (45) OECD (2020) (46), Office for National Statistics (2022) (47)	Mechanically ventilated COVID-19 patients in England
Population parameters	Age[2]	61	NA	NA	Docherty et al. (2020) (48)	Mechanically ventilated COVID-19 patients in the United Kingdom
	Female	30.2%	NA	NA	Shryane et al. (2021) (49)	English ICU COVID-19 patients
In hospital parameters	Length of stay general ward[3]	2.90	10%*base case: 0.29	Gamma	Shryane et al. (2021) (49)	English ICU COVID-19 patients
	Length of stay ICU not mechanically ventilated[3]	3.71	10%*base case: 0.37	Gamma	Shryane et al. (2021) (49)	English ICU COVID-19 patients
	Duration of mechanical ventilation[3]	7.79	10%*base case: 0.78	Gamma	Shryane et al. (2021) (49)	English ICU COVID-19 patients
	In-hospital mortality	32%	0.07	Beta	Wang et al. (2021) (50)	English ICU COVID-19 patients

First six months after hospital admission	Six months mortality	6.25%	0.03	Beta	Garfield et al. (2021) (51)	COVID-19 veno-venous extracorporeal membrane oxygenation patients in the UK
Life expectancy	Life expectancy female of age 61	24.56	NA	NA	Office of National Statistics (2021) (52)	English general population
	Life expectancy male of age 61	21.87	NA	NA	Office of National Statistics (2021) (52)	English general population
Utilities	Healthy stage 55 -64 female[4A]	0.804	0.30	Beta	Szende et al., 2014 (37)	England general female population
	Healthy stage 65-74 female[4A]	0.760	0.29	Beta	Szende et al., 2014 (37)	England general female population
	Healthy stage 75+ female[4A]	0.692	0.31	Beta	Szende et al., 2014 (37)	England general female population
	Healthy stage 55-64 male[4A]	0.833	0.27	Beta	Szende et al., 2014 (37)	England general male population
	Healthy stage 65-74 male[4A]	0.810	0.27	Beta	Szende et al., 2014 (37)	England general male population
	Healthy stage 75+ male[4A]	0.753	0.26	Beta	Szende et al., 2014 (37)	England general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	117.61	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above
	General ward per day[4B]	273.72	10%*base case: 27.37	Gamma	National Health Services (2020-2021) (53), Office of national statistics (54) Eurostat (31), OECD (34)	United Kingdom Non-elective long stay, COVID-19 patients over 19
	ICU not mechanically ventilated per day[4B]	1525.49	10%*base case: 152.55	Gamma	National Health Services (2020-2021) (53), Eurostat (31), OECD (34)	United Kingdom ICU patients with zero organs supported

	Mechanically ventilated per day[4B]	1,299.34	10%*base case: 129.93	Gamma	National Health Services (2020-2021) (53), Eurostat (31), OECD (34)	United Kingdom ICU patients with one organ supported

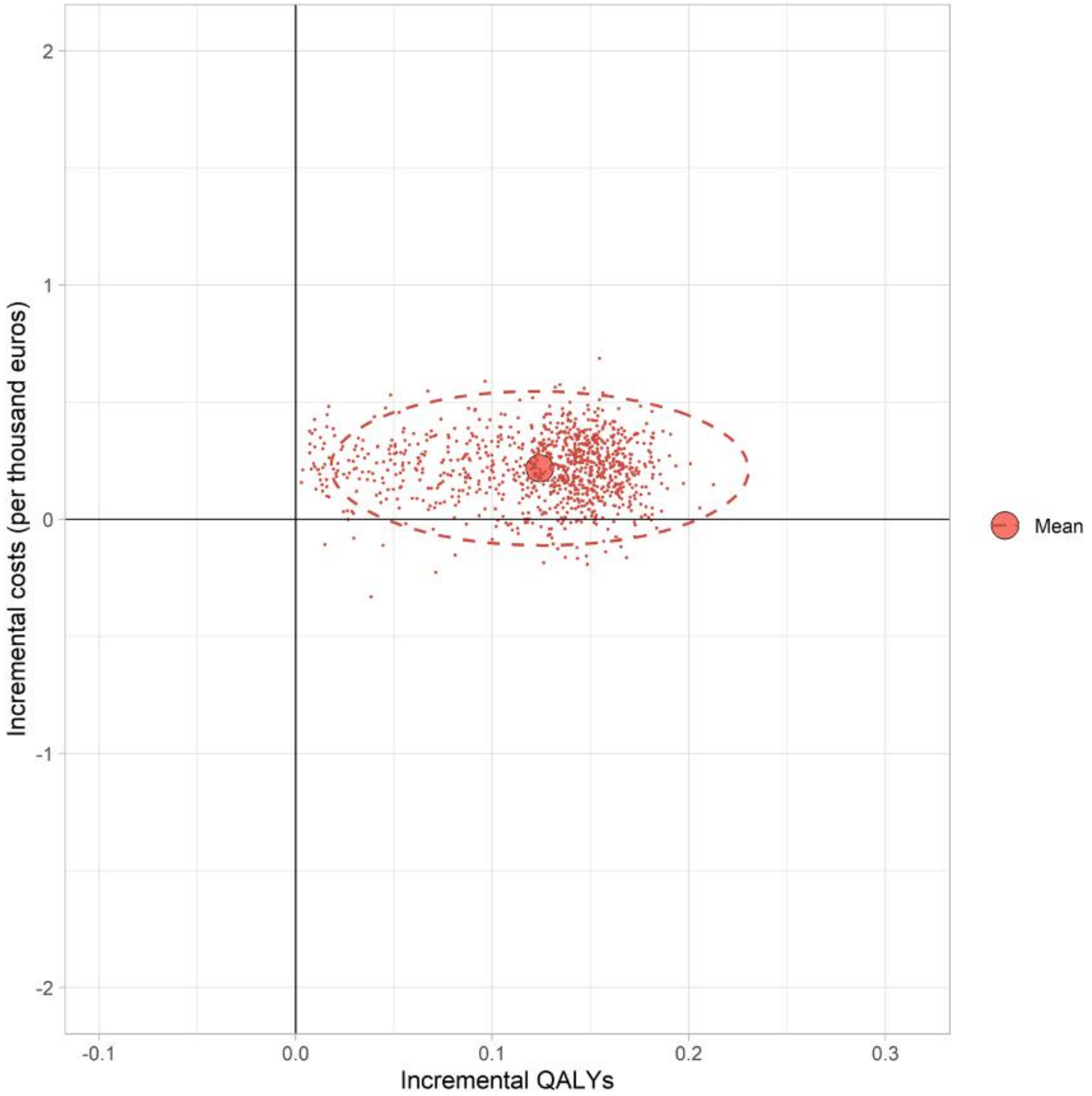
1. Mechanically ventilated ICU occupancy was calculated by taking the average number of occupied COVID-19 mechanically ventilated beds in 2022 (45) and dividing this by the number of ICU beds with mechanical ventilation equipment (46,47).
2. Assuming a normal distribution for age. Hence, the mean equals the median
3. Estimated using a total intensive care length of stay in England of 11.5 and keeping the ratios of the German base case fixed between the different substages.
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

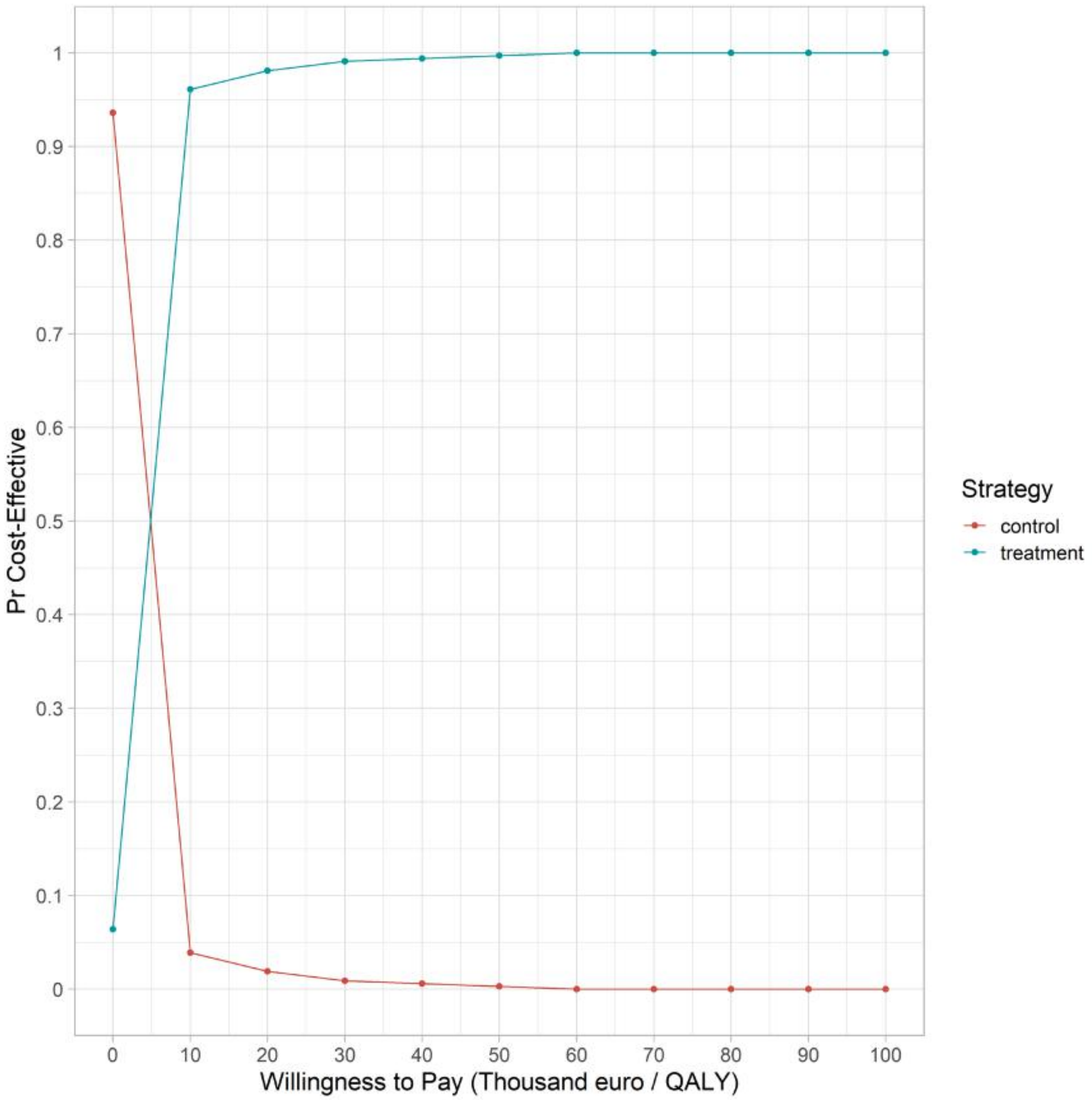
7.1.2 Results

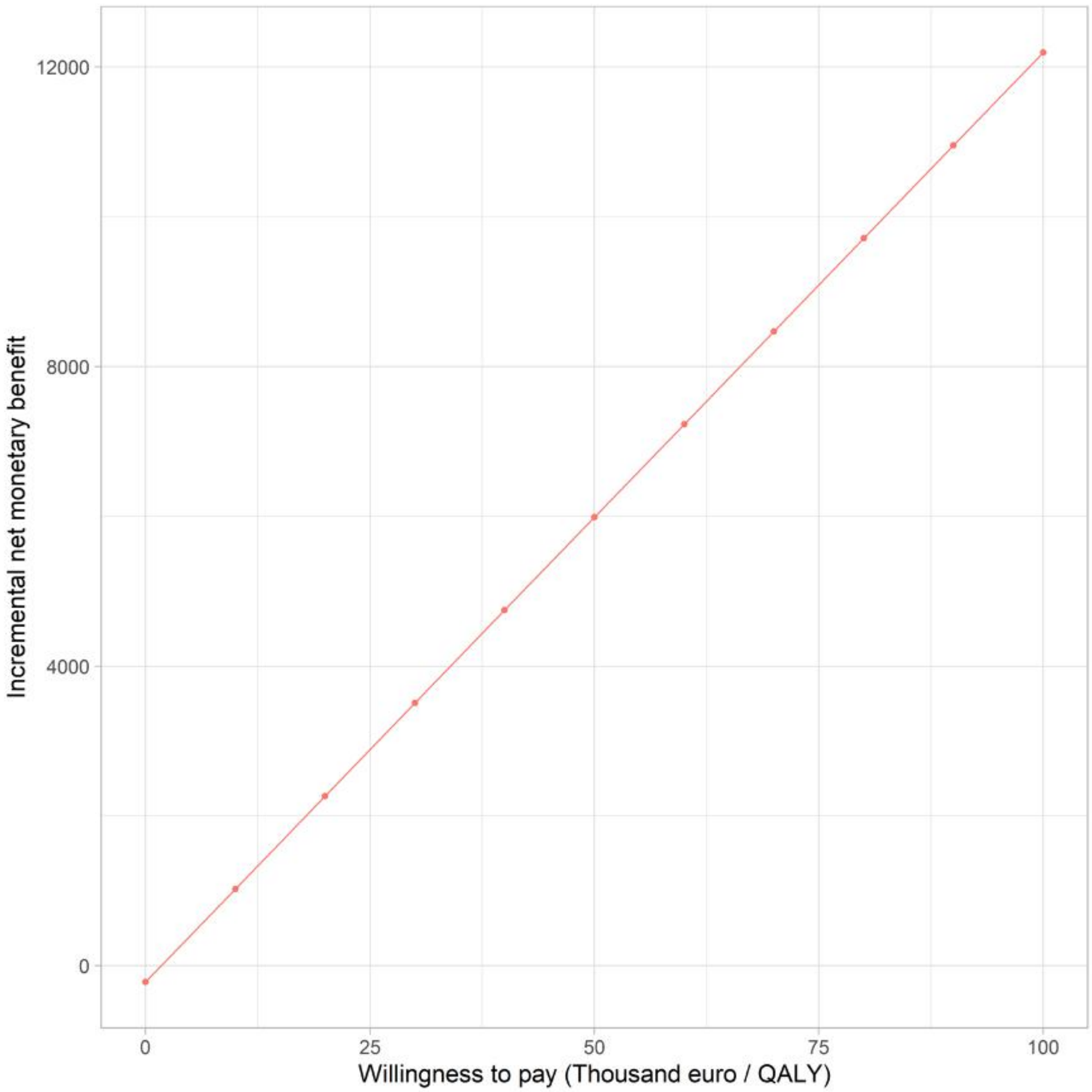
7.1.2.1 Base case

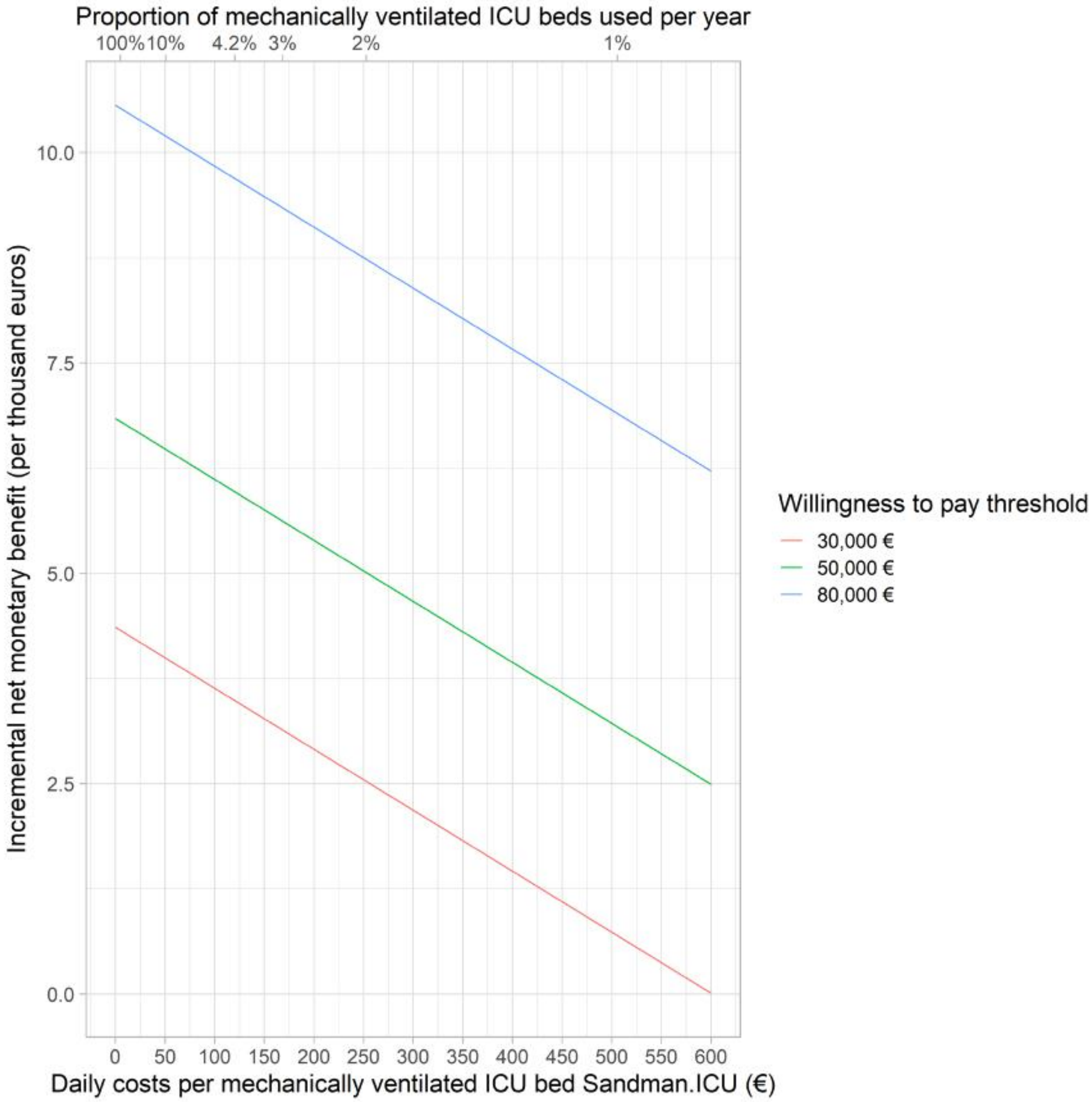
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
61	Care as usual	17,875.12	8.54	NA	NA	NA	NA
61	Treatment	18,099.53	8.67	224.41	0.13	1,775.13	3,490.50
65	Care as usual	17,875.12	7.36	NA	NA	NA	NA
65	Treatment	18,099.53	7.47	224.41	0.11	2,055.69	2,983.49
70	Care as usual	17,875.12	5.77	NA	NA	NA	NA
70	Treatment	18,099.53	5.86	224.41	0.09	2,616.34	2,296.07

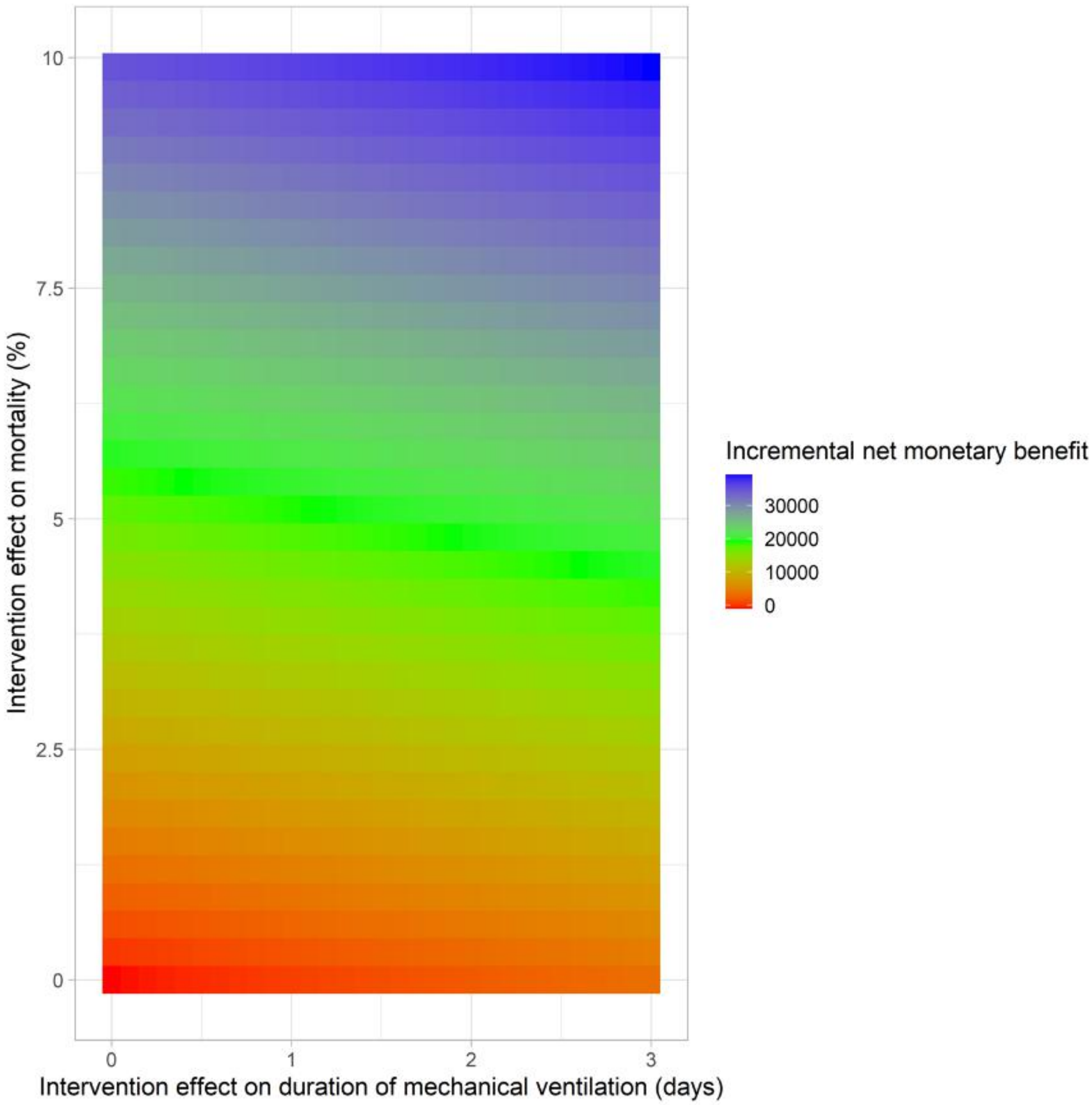
7.1.2.2 PSA result




Pr Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


12000
8000
4000
0
Incremental net monetary benefit
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
10.0
7.5
5.0
2.5
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


Intervention effect on mortality (%)
10
7.5
5
2.5
0
Intervention effect on duration of mechanical ventilation (days)
0
1
2
3
Incremental net monetary benefit
30000
20000
10000
0

7.2 Hungary

7.2.1 Parameters

Group of parameters	Parameter	Base case (i.e. mean)	Standard deviation	Distribution probabilistic sensitivity analysis	Source	Studied population in source
Country specific parameters	Willingness to pay	3 times GDP per capita: 73,116.51	NA	NA	Kovács et al. (2022) (55), The world bank (2021) (56) Eurostat (31)	NA
	Mechanical ventilated ICU occupancy[1]	40.0%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), OECD (2020) (46), the world bank (2021) (57) Uusküla et al., 2022 (58) Benes et al., 2022 (59)	Hospitalized COVID-19 patients in Hungary, COVID-19 ICU admission in Estonia and mechanical ventilated COVID-19 patients in eastern Europe
Population parameters	Age[2]	68	NA	NA	Benes et al. (2022) (59)	COVID-19 ICU patients in Eastern Europe
	Female	32.3%	NA	NA	Benes et al. (2022) (59)	COVID-19 ICU patients in Eastern Europe
In hospital parameters	Length of stay general ward[3]	2.94	10% base case: 0.29	Gamma	Benes et al. (2022) (59)	Eastern European COVID-19 ICU patients
	Length of stay ICU not mechanically ventilated[3]	2.62	10% base case: 0.26	Gamma	Benes et al. (2022) (59), data reported by SE	Eastern European COVID-19 ICU patients
	Duration of mechanical ventilation[3]	9.02	10% base case: 0.90	Gamma	Benes et al. (2022) (59), data reported by SE	Eastern European COVID-19 ICU patients

	In-hospital mortality	66.35%	0.015	Beta	Benes et al. (2022) (59)	Eastern European mechanically ventilated COVID-19 patients
Life expectancy	Life expectancy female of age 68	14.5	NA	NA	OECD (2021) (60)	Hungarian general population
	Life expectancy male of age 68	10.4	NA	NA	OECD (2021) (60)	Hungarian general population
Utilities	Healthy stage 65-74 female[4,5A]	0.687	0.26	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 75+ female[4,5A]	0.626	0.27	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 65-74 male[4,5A]	0.762	0.27	Beta	Szende et al., 2014 (37)	Hungarian general male population
	Healthy stage 75+ male[4,5A]	0.666	0.28	Beta	Szende et al., 2014 (37)	Hungarian general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	12.64	NA	NA	See section 2.4.1, Eurostat (38)	Calculated using ICU occupancy above

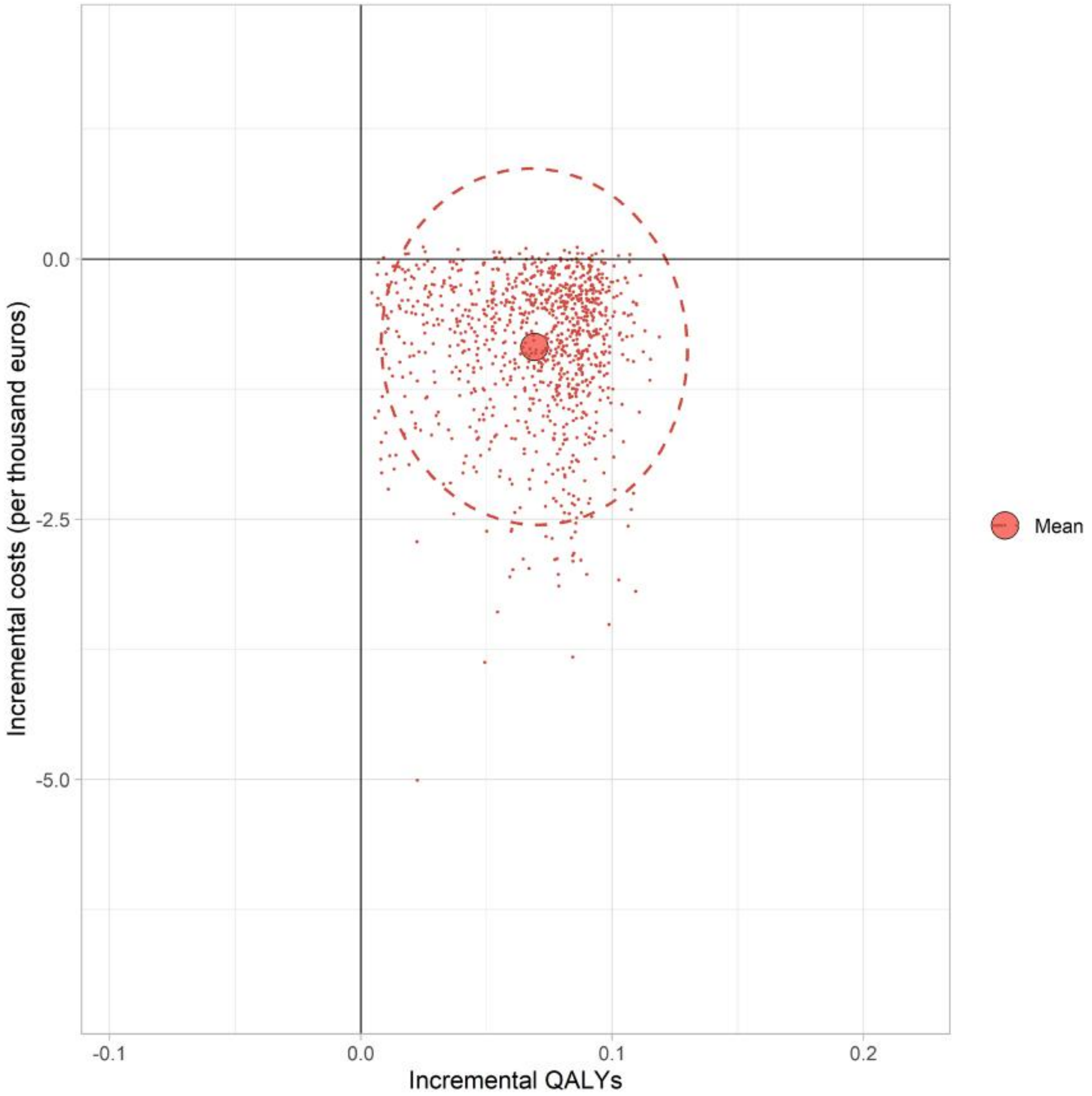
1. Hospital occupancy in Hungary was obtained from European Centre for Disease Prevention and Control, 2022 (29), which was on average 3006.80 occupied hospital beds. This was multiplied with the proportion of ICU patients (Uusküla et al., 2022 (58)) and the proportion of mechanically ventilated patients (Benes et al., 2022 (59)) and subsequently divided by the number of ICU beds with mechanical ventilation available (i.e. 1088 beds).
2. Assuming a normal distribution for age. Hence, the mean equals the median
3. Estimated mean total intensive care length of stay in Eastern Europe using data from Benes et al. (2022)(59) and method of moments, this was multiplied with the ratio intensive care length of stay and duration of mechanical ventilation. Ratio intensive care length of stay and mechanical ventilation duration was obtained from data from partner SE. Ratios between general ward length of stay and intensive care length of stay were taken from the German base case.
4. Taken with EQ-5D index value (European VAS value set).
5. In the PSA ratios were kept fixed between these variables (grouped with letters).

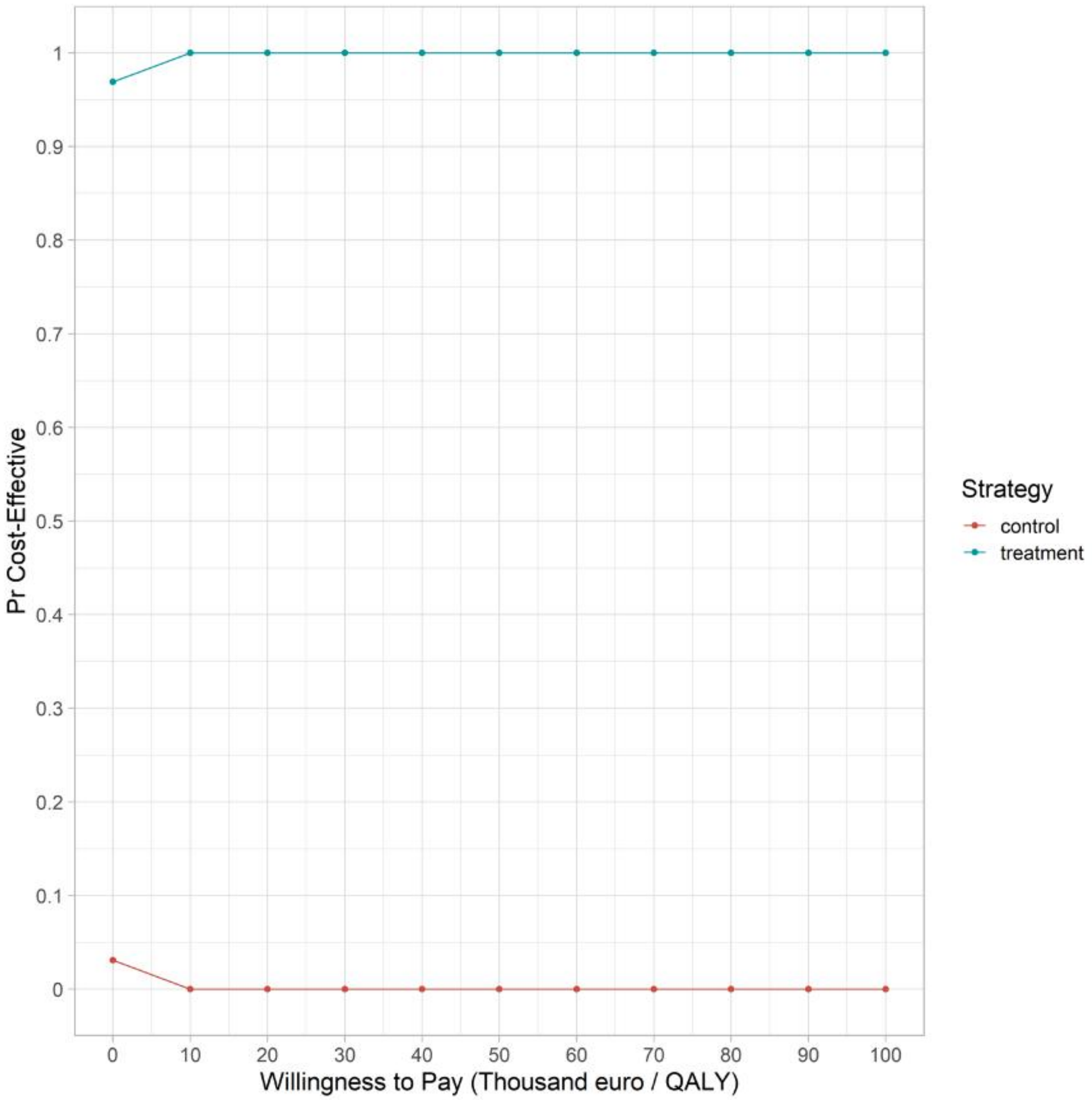
7.2.2 Results

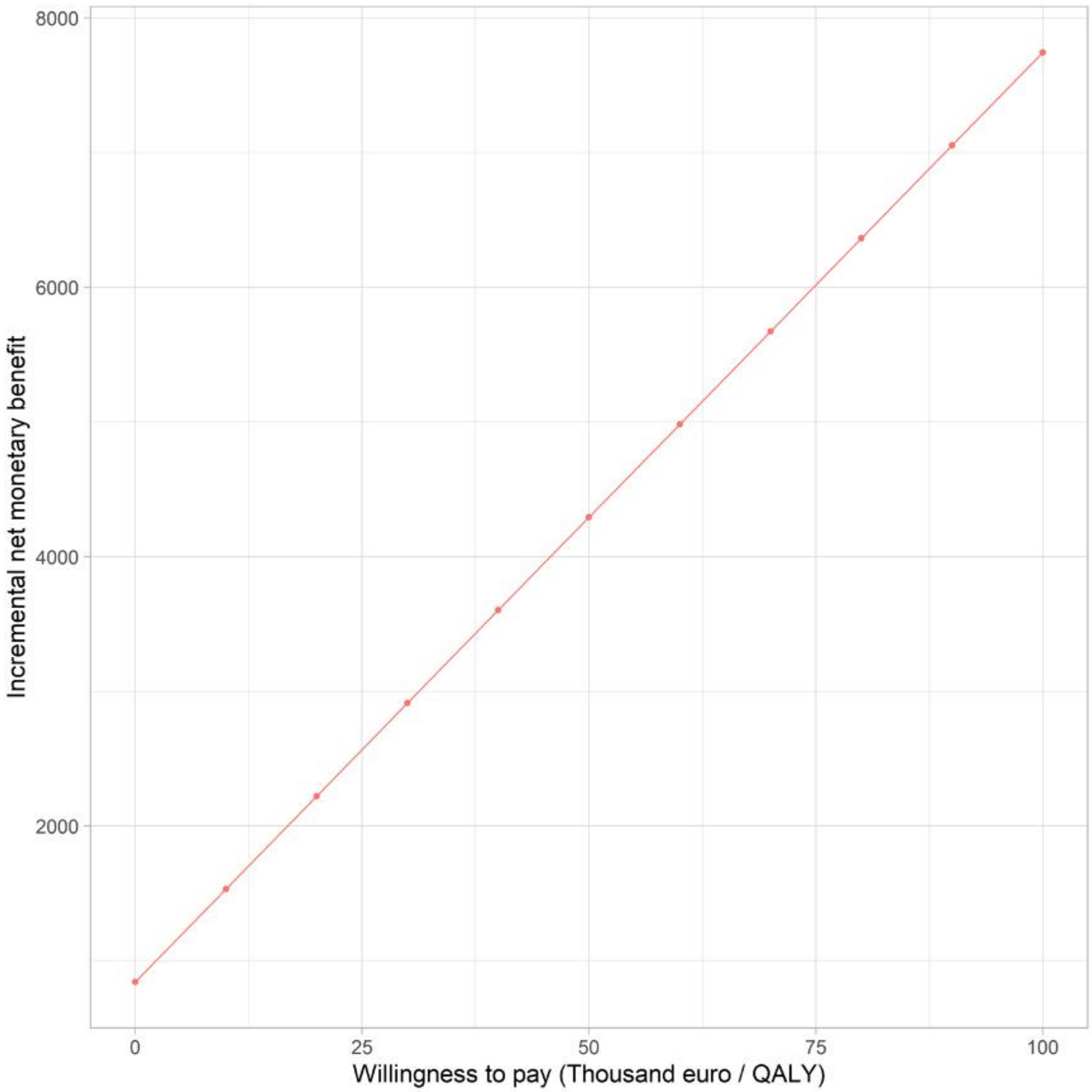
7.2.2.1 *Base case*

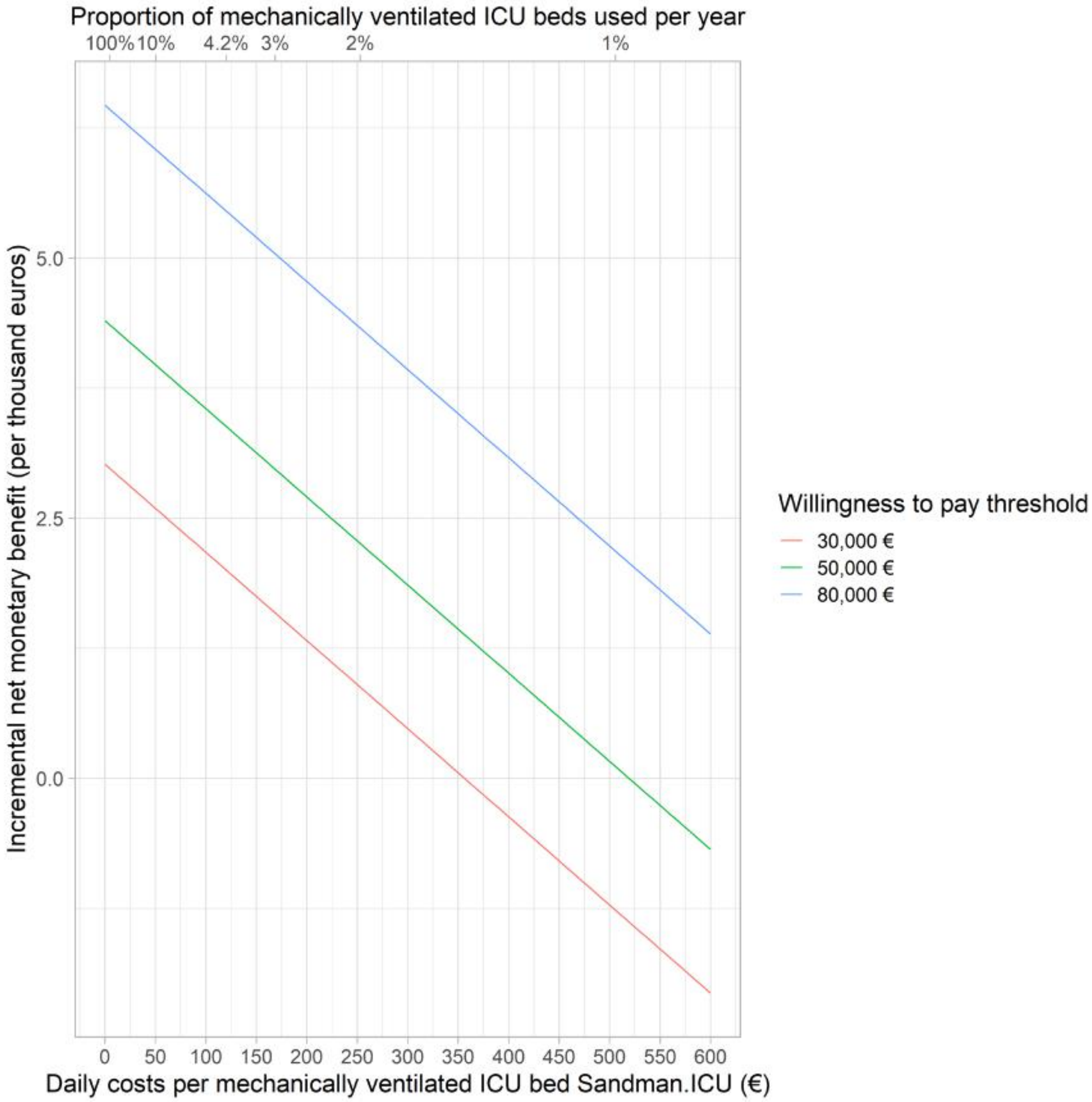
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	22,006.35	3.59	NA	NA	NA	NA
60	Treatment	21,130.50	3.70	-875.85	0.11	-8,173.45	8,710.87
65	Care as usual	22,006.35	2.84	NA	NA	NA	NA
65	Treatment	21,130.50	2.92	-875.85	0.08	-10,331.99	7,073.99
68	Care as usual	22,006.35	2.36	NA	NA	NA	NA
68	Treatment	21,130.50	2.43	-875.85	0.07	-12,406.28	6,037.68

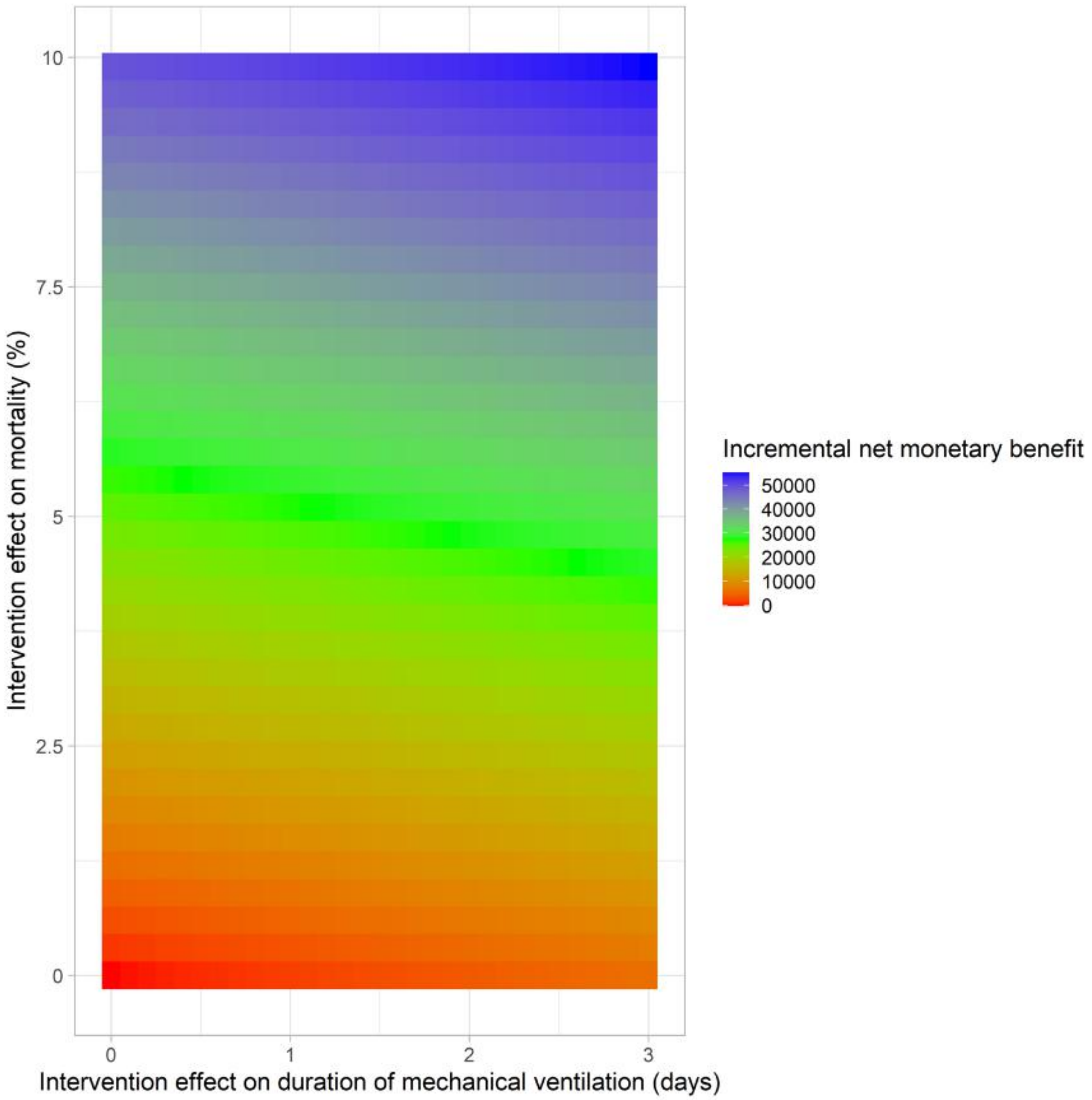
7.2.2.2 PSA results




Pr Cost-Effective
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


8000
6000
4000
2000
Incremental net monetary benefit
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
5.0
2.5
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


Intervention effect on mortality (%)
10
7.5
5
2.5
0
0
1
2
3
Intervention effect on duration of mechanical ventilation (days)
Incremental net monetary benefit
50000
40000
30000
20000
10000
0

7.3 Italy

7.3.1 Parameters

Group of parameters	Parameter	Base case (i.e. mean)	Standard deviation	Distribution probabilistic sensitivity analysis	Source	Studied population in source
Country specific parameters	Willingness to pay	€ 61,430.22	NA	NA	Cf. Ghetti et al. (2021) (61)	NA
	Mechanical ventilated ICU occupancy[1]	5.4%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), Grasselli et al. (2020) (62), Gitto (2021) (63), The world bank (2021)(64)	COVID-19 ICU patients in Italy
Population parameters	Age[2]	64	NA	NA	Grasselli et al. (2020) (62)	COVID-19 ICU patients in Italy
	Female	20.1%	NA	NA	Grasselli et al. (2020) (62)	COVID-19 ICU patients in Italy
In hospital parameters	Length of stay general ward[3]	15.59	10%* base case: 1.56	Gamma	Grasselli et al. (2020) (62)	COVID-19 ICU patients in Italy
	Length of stay ICU not mechanically ventilated[3]	2.83	10%*base case: 0.28	Gamma	Grasselli et al. (2020) (62)	COVID-19 ICU patients in Italy
	Duration of mechanical ventilation[3]	11.91	10%*base case: 1.19	Gamma	Grasselli et al. (2020) (62)	COVID-19 ICU patients in Italy
	In-hospital mortality	48.3%	0.008	Beta	Grasselli et al. (2020) (62)	Italian COVID-19 ICU patients
Life expectancy	Life expectancy female of age 64	23.3	NA	NA	OECD (2021) (60)	Italian general female population
	Life expectancy male of age 64	20.0	NA	NA	OECD (2021) (60)	Italian general male population
Utilities	Healthy stage 55-64 female[4A]	0.929	0.10	Beta	Szende et al., 2014 (37)	Italian general female population

	Healthy stage 65-74 female4A	0.879	0.17	Beta	Szende et al., 2014 (37)	Italian general female population
	Healthy stage 75+ female4A	0.817	0.20	Beta	Szende et al., 2014 (37)	Italian general female population
	Healthy stage 55-64 male4A	0.944	0.11	Beta	Szende et al., 2014 (37)	Italian general male population
	Healthy stage 65-74 male4A	0.935	0.10	Beta	Szende et al., 2014 (37)	Italian general male population
	Healthy stage 75+ male4A	0.880	0.14	Beta	Szende et al., 2014 (37)	Italian general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	93.65€	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above
	General ward per day4B	493.77	10%* base case: 49.38	Gamma	Foglia et al. (2022)(65) Eurostat (31)	Italian COVID-19 low complexity patients
	ICU not mechanically ventilated per day4B	726.56	10%*base case: 72.66	Gamma	Foglia et al. (2022)(65) Eurostat (31)	Italian COVID-19 medium complexity patients
	Mechanically ventilated per day4B	1454.42	10%*base case: 145.44	Gamma	Foglia et al. (2022)(65) Eurostat (31)	Italian COVID-19 mechanically ventilated patients

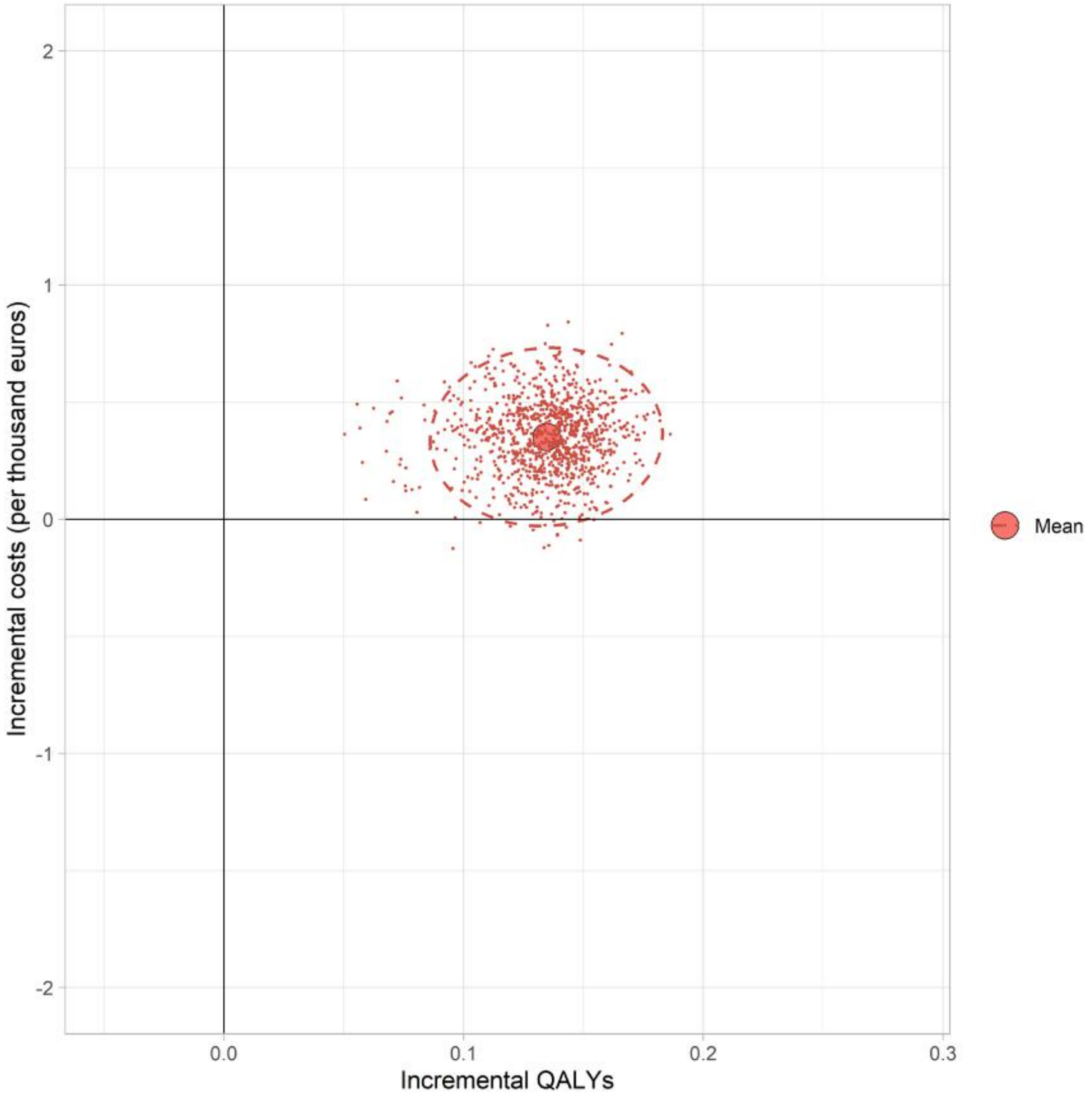
1. Number of weekly Italian COVID-19 ICU admissions in 2022 were obtained from European Centre for Disease Prevention and Control, 2022. Taking into account a mean intensive care length of stay of 14.73 days (62) and 14.8 ICU beds per 100,000 inhabitants (63,64), we obtained the ICU occupancy, which was 6.1%. Taking into account that 88% of patients get mechanically ventilated (62) the estimated mechanically ventilated COVID-19 ICU occupancy in 2022 was: 5.4%.
2. Assuming a normal distribution for age. Hence, median equals the mean.
3. Estimated using a total intensive care length of stay in Italy of 9 days (62) and keeping the ratios of the German base case fixed between the different substages.
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

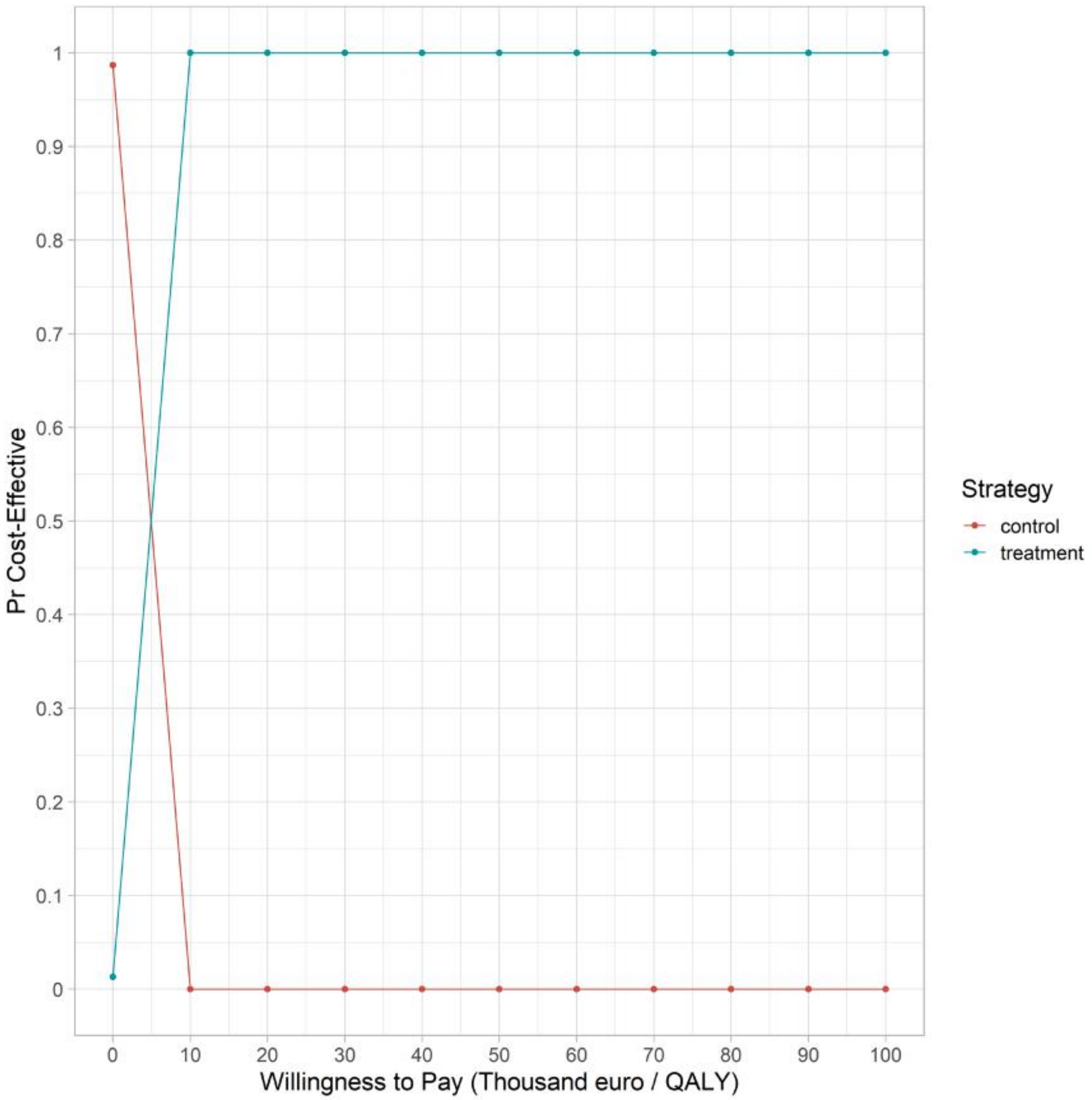
7.3.2 Results

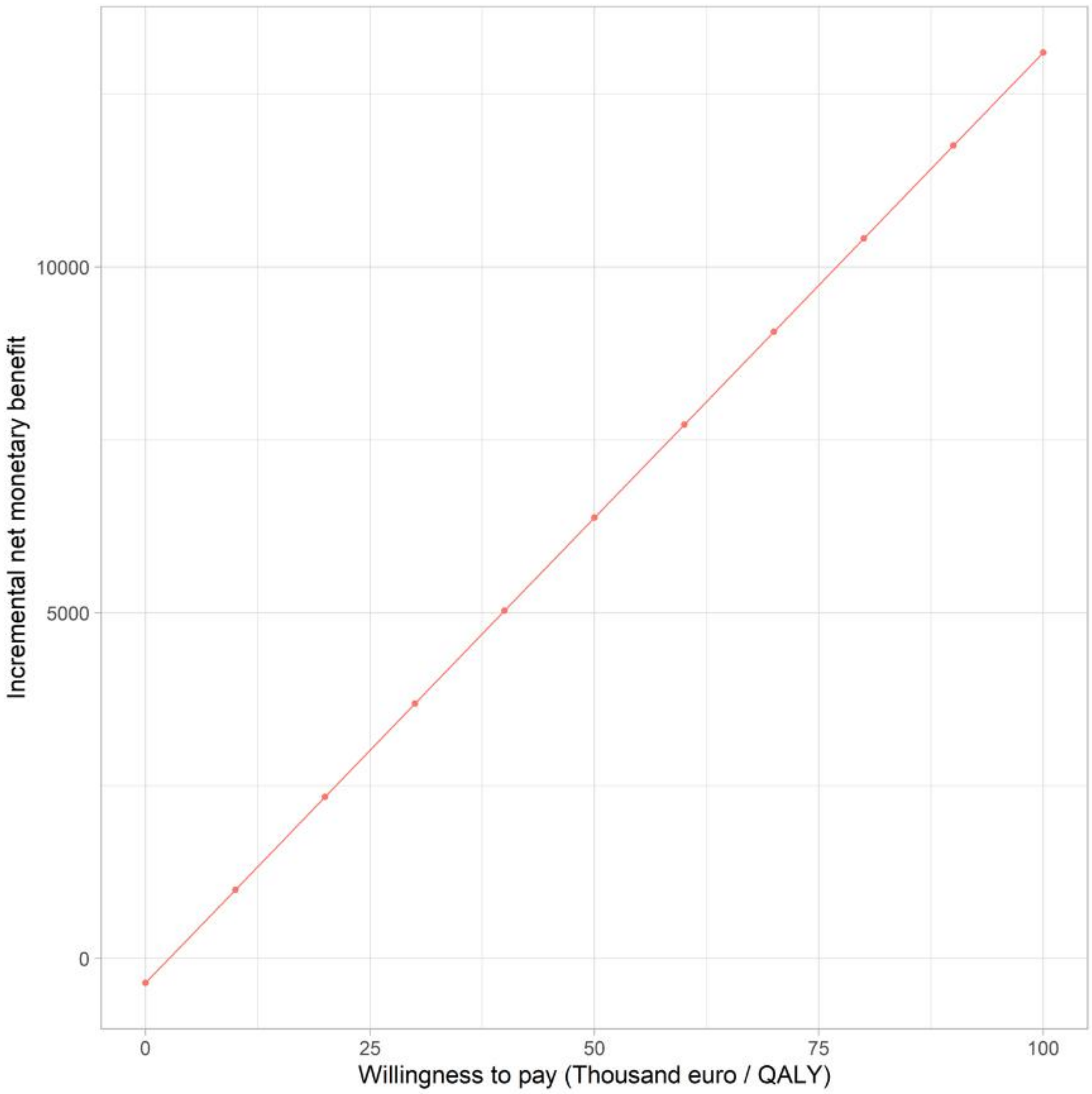
7.3.2.1 *Base case*

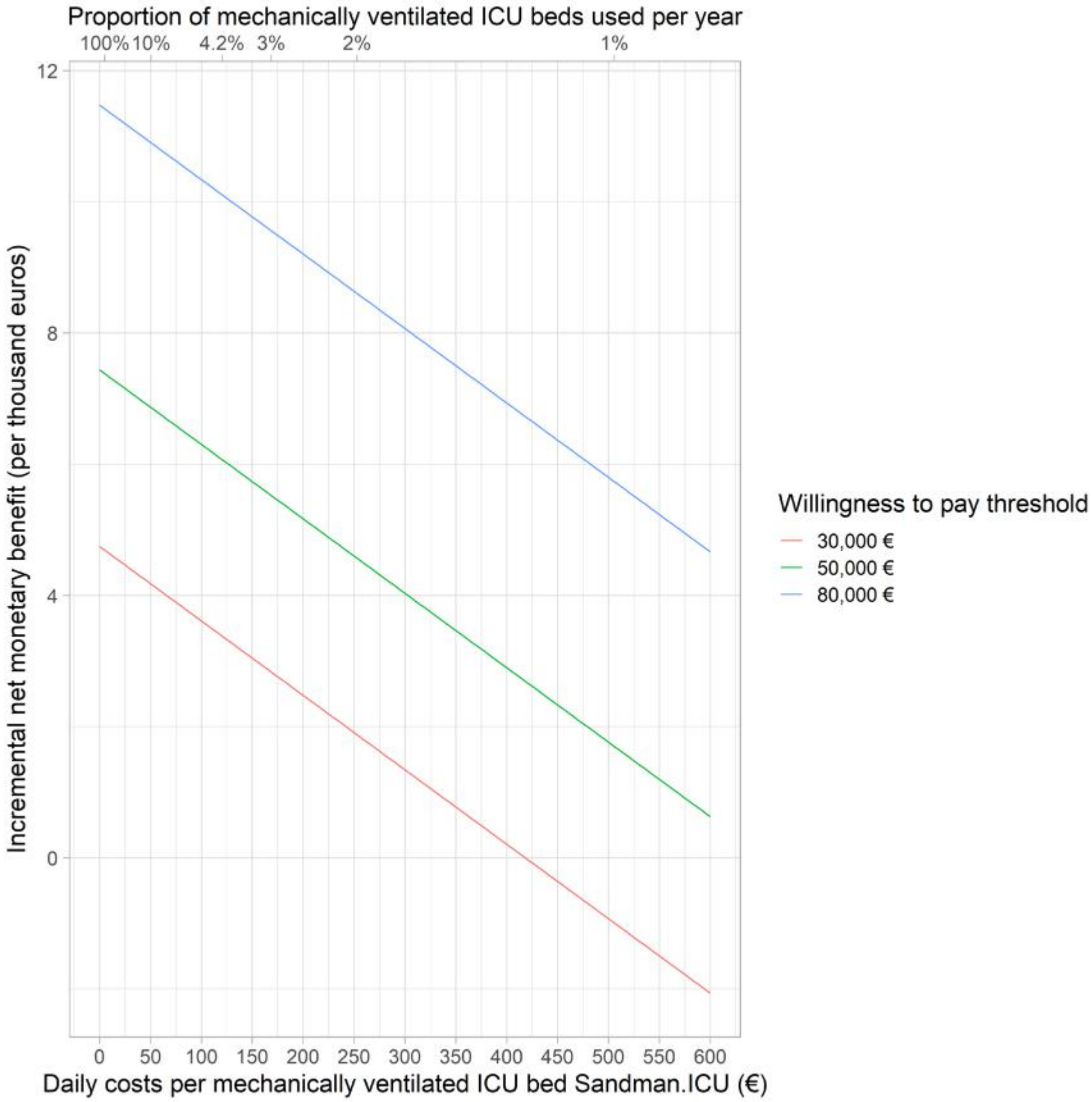
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	28,107.94	7.98	NA	NA	NA	NA
60	Treatment	28,467.56	8.13	359.61	0.15	2,331.27	9,116.33
64	Care as usual	28,107.94	7.02	NA	NA	NA	NA
64	Treatment	28,467.56	7.15	359.61	0.14	2,649.20	7,979.14
70	Care as usual	28,107.94	5.40	NA	NA	NA	NA
70	Treatment	28,467.56	5.51	359.61	0.10	3,440.65	6,060.97

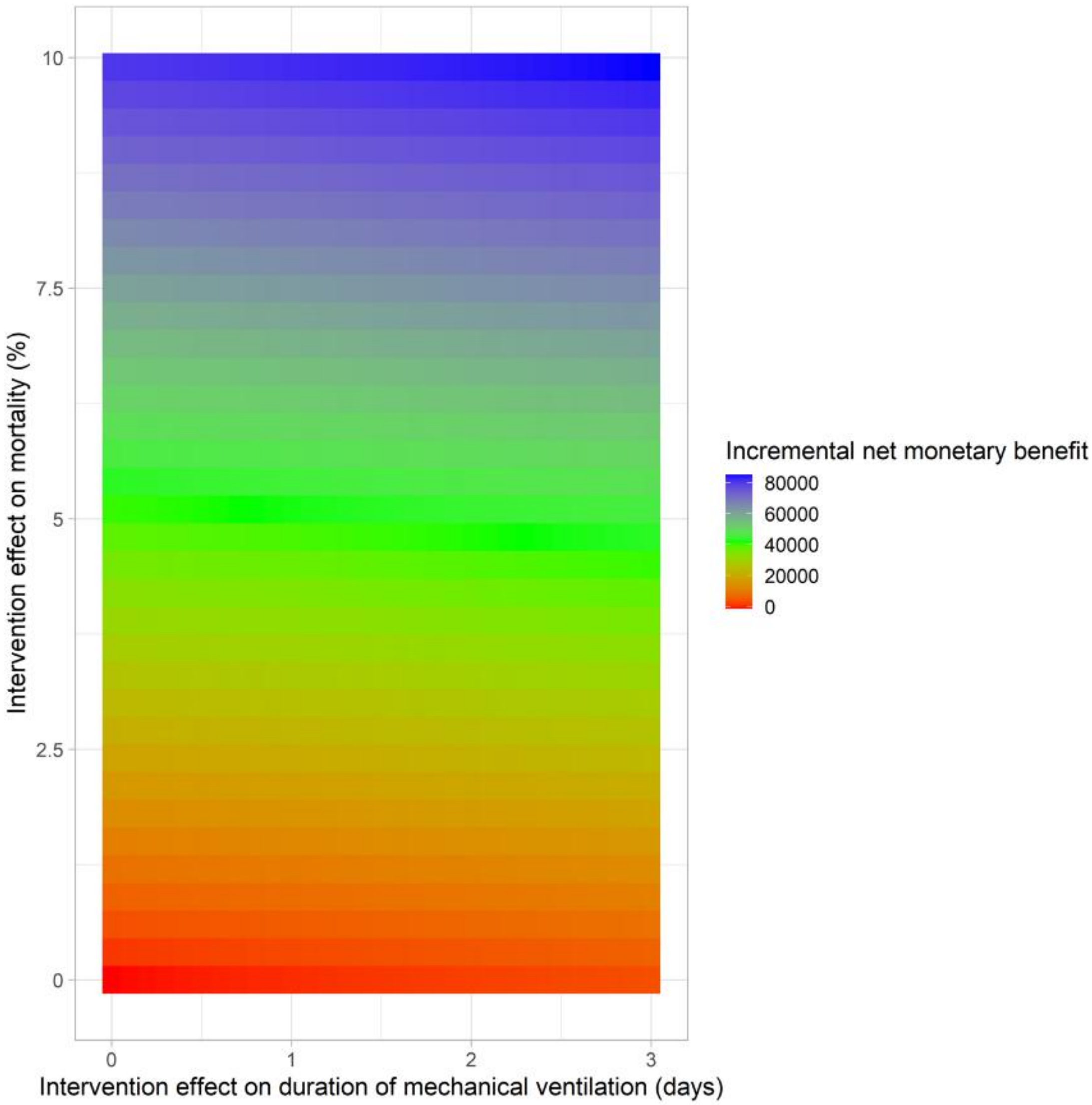
7.3.2.2 PSA results




Pr Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


Incremental net monetary benefit
10000
5000
0
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
12
8
4
0
Incremental net monetary benefit (per thousand euros)
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


10
7.5
5
2.5
0
Intervention effect on mortality (%)
0
1
2
3
Intervention effect on duration of mechanical ventilation (days)
Incremental net monetary benefit
80000
60000
40000
20000
0

7.4 Lithuania

7.4.1 Parameters

Group of parameters	**Parameter**	**Base case (i.e. mean)**	**Standard deviation**	**Distribution probabilistic sensitivity analysis**	**Source**	**Studied population in source**
Country specific parameters	Willingness to pay	3 times GDP per capita: 84,712.49	NA	NA	Kovács et al. (2022) (55), The world bank (2021) (66) Eurostat (31)	NA
	Mechanical ventilated ICU occupancy[1]	11.4%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), Rhodes et al. (2012) (67) Uusküla et al., 2022 (58) Benes et al., 2022 (59)	Hospitalized COVID-19 patients in 2022 in Lithuania, COVID-19 ICU admission in Estonia and mechanical ventilated COVID-19 patients in eastern Europe
Population parameters	Age[2]	68	NA	NA	Benes et al. (2022) (59)	COVID-19 ICU patients in Eastern Europe
	Female	32.3%	NA	NA	Benes et al. (2022) (59)	COVID-19 ICU patients in Eastern Europe
In hospital parameters	Length of stay general ward[3]	2.94	10% base case: 0.29	Gamma	Benes et al. (2022) (59)	Eastern european COVID-19 ICU patients
	Length of stay ICU not mechanically ventilated[3]	2.62	10% base case: 0.26	Gamma	Benes et al. (2022) (59), data reported by SE	Eastern european COVID-19 ICU patients
	Duration of mechanical ventilation[3]	9.02	10% base case: 0.90	Gamma	Benes et al. (2022) (59), data reported by SE	Eastern european COVID-19 ICU patients
	In-hospital mortality	66.35%	0.015	Beta	Benes et al. (2022) (59)	Eastern European mechanically ventilated COVID-19 patients

Life expectancy	Life expectancy female of age 68	15.3	NA	NA	OECD (2021) (60)	Lithuanian general female population
	Life expectancy male of age 68	10.2	NA	NA	OECD (2021) (60)	Lithuanian general male population
Utilities	Healthy stage 65-74 female[4,5A]	0.687	0.26	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 75+ female[4,5A]	0.626	0.27	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 65-74 male[4,5A]	0.762	0.27	Beta	Szende et al., 2014 (37)	Hungarian general male population
	Healthy stage 75+ male[4,5A]	0.666	0.28	Beta	Szende et al., 2014 (37)	Hungarian general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	44.36	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above

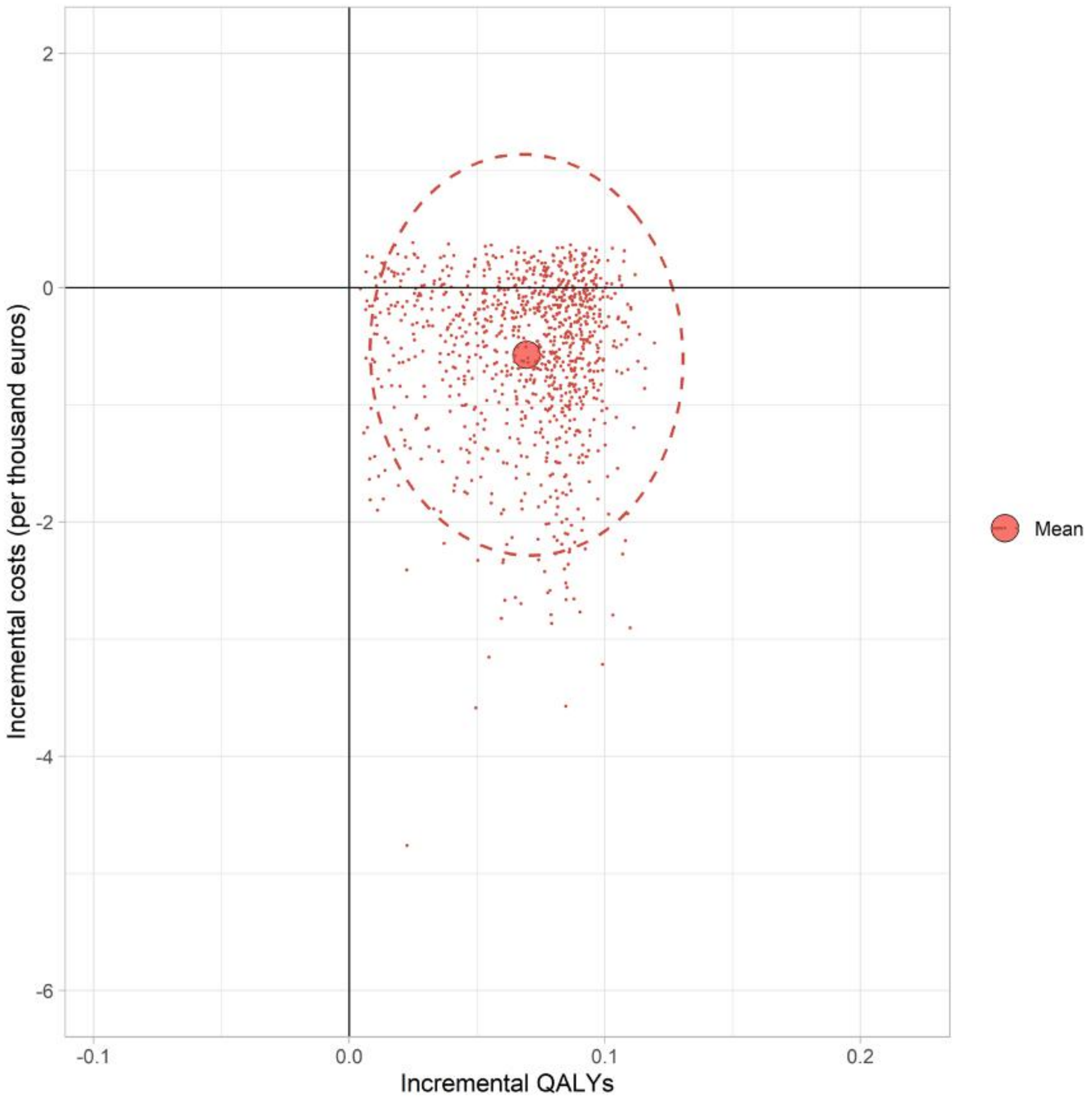
1. Hospital occupancy in Lithuania was obtained from European Centre for Disease Prevention and Control, 2022 (29), which was on average 390.67 occupied hospital beds. We multiplied this with the proportion of ICU patients (Uusküla et al., 2022 (58)) and the proportion of mechanically ventilated patients (Benes et al., 2022 (59)) and subsequently dividing this by the number of ICU beds available (67).
2. Assuming a normal distribution for age. Hence, the mean equals the median.
3. Estimated mean total intensive care length of stay in Eastern Europe using data from Benes et al. (2022)(59) and method of moments, this was multiplied with the ratio intensive care length of stay and duration of mechanical ventilation. Ratio intensive care length of stay and mechanical ventilation duration was obtained from data from partner SE. Ratios between general ward length of stay and intensive care length of stay were taken from the German base case.
4. Taken with EQ-5D index value (European VAS value set).
5. In the PSA ratios were kept fixed between these variables (grouped with letters).

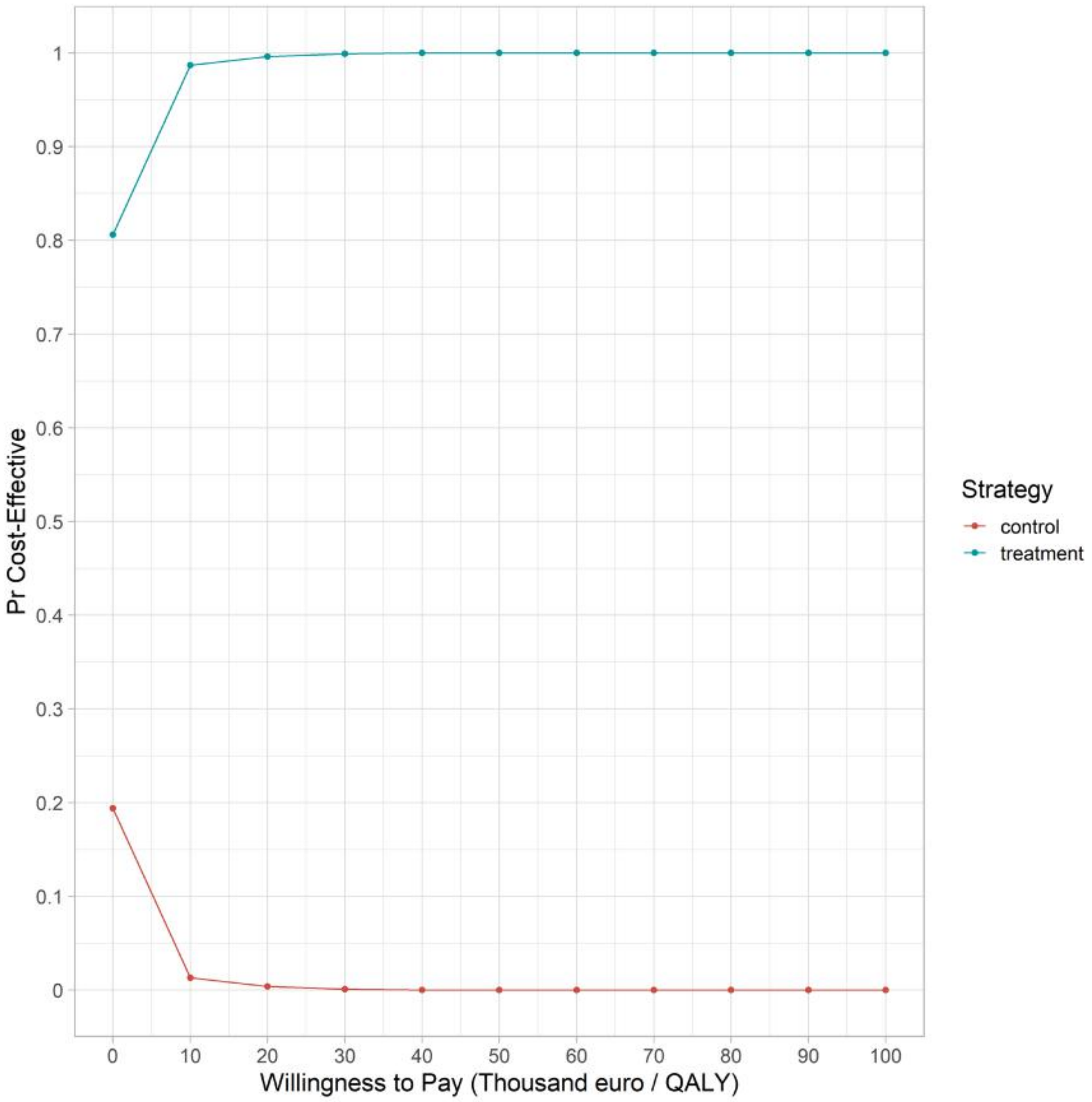
7.4.2 Results

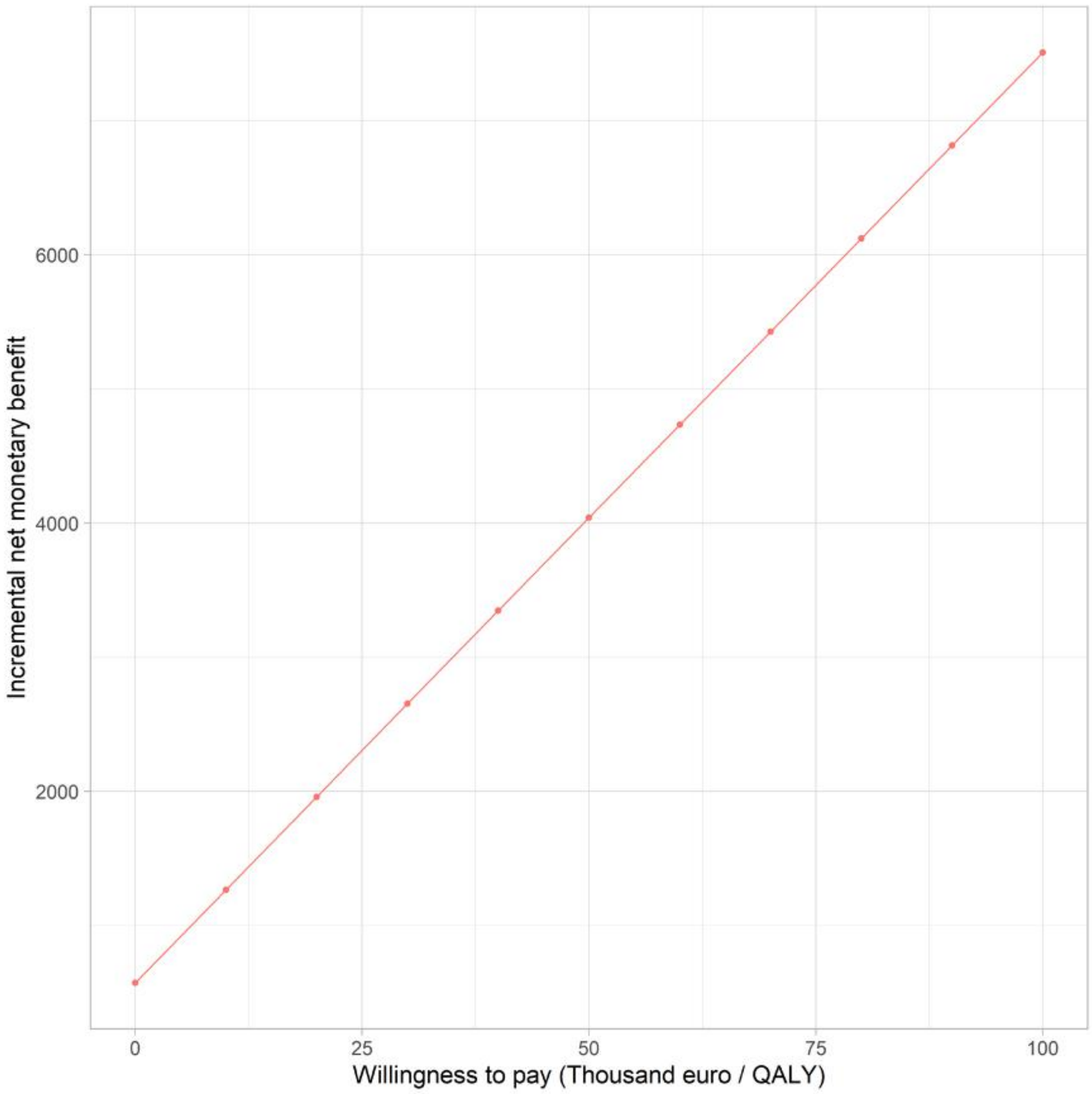
7.4.2.1 Base case

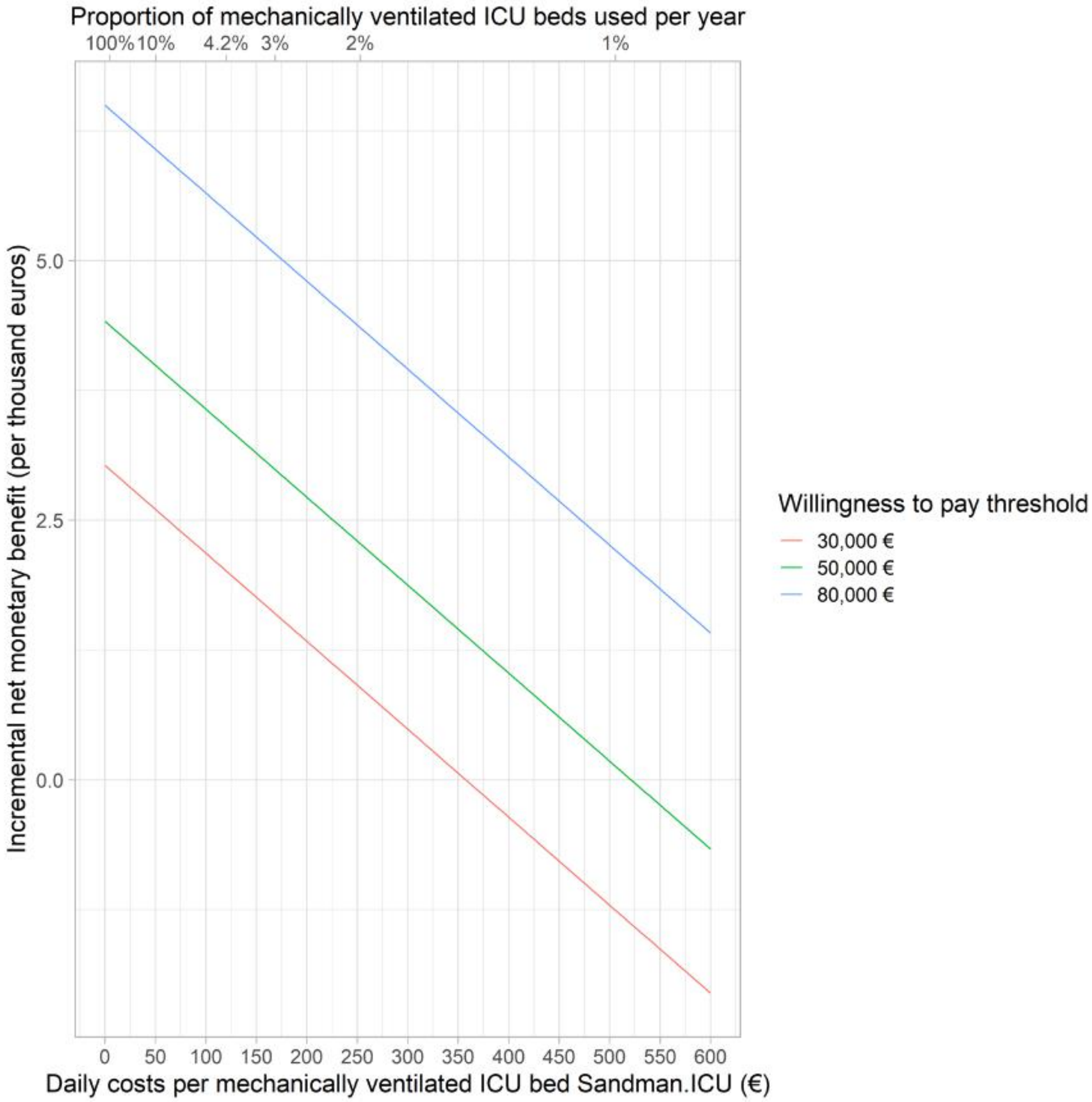
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	22,006.35	3.60	NA	NA	NA	NA
60	Treatment	21,400.75	3.71	-605.6	0.11	-5,636.88	9,706.78
65	Care as usual	22,006.35	2.85	NA	NA	NA	NA
65	Treatment	21,400.75	2.93	-605.6	0.09	-7,116.97	7,814.05
68	Care as usual	22,006.35	2.37	NA	NA	NA	NA
68	Treatment	21,400.75	2.44	-605.6	0.07	-8,535.71	6,615.91

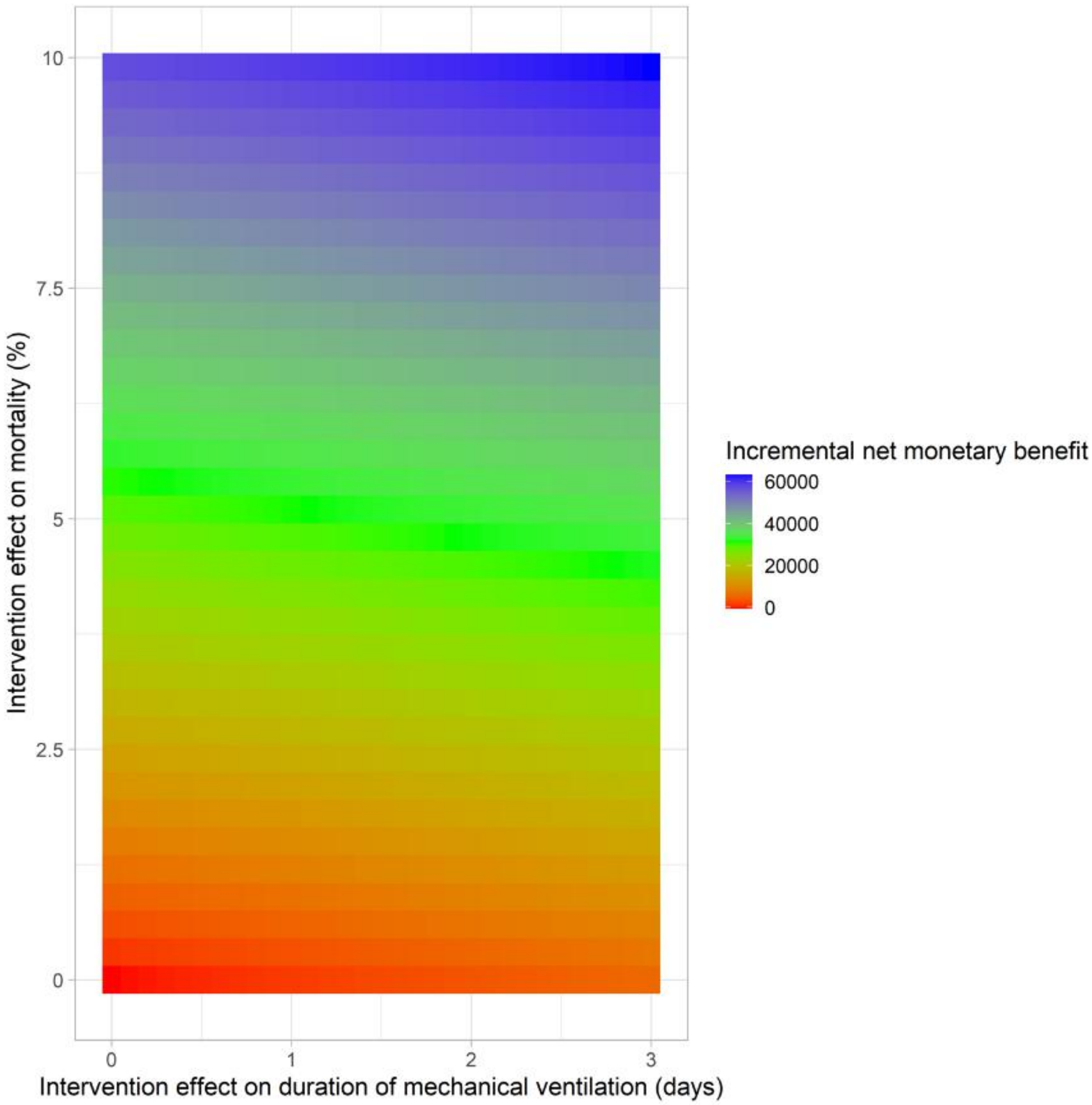
7.4.2.2 PSA results




1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Pr Cost-Effective
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


Incremental net monetary benefit
6000
4000
2000
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
5.0
2.5
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


Intervention effect on mortality (%)
10
7.5
5
2.5
0
0
1
2
3
Intervention effect on duration of mechanical ventilation (days)
Incremental net monetary benefit
60000
40000
20000
0

7.5 Portugal

7.5.1 Parameters

Group of parameters	**Parameter**	**Base case (i.e. mean)**	**Standard deviation**	**Distribution probabilistic sensitivity analysis**	**Source**	**Studied population in source**
Country specific parameters	Willingness to pay	2 times GDP per capita: 47,479.46	NA	NA	Marques et al. (2016) (68), The world bank (2021) (69) Eurostat (2021) (31)	NA
	Mechanical ventilated ICU occupancy[1]	26.8%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), Rhodes et al. (2012) (67), Ribeiro-Queirós et al. (2021) (70)	COVID-19 ICU patients in Portugal
Population parameters	Age[2]	63	NA	NA	Ribeiro-Queirós et al. (2021) (70)	COVID-19 ICU patients in Portugal
	Female	34.3%	NA	NA	Ribeiro-Queirós et al. (2021) (70)	COVID-19 ICU patients in Portugal
In hospital parameters	Length of stay general ward	14.06	19.54	Gamma	Data ICU COVID-19 patients of partner ICS-HUB	500 ICU COVID-19 patients of partner ICS-HUB, Spain
	Length of stay ICU not mechanically ventilated[3]	5.14	10*base case: 0.51	Gamma	Ribeiro-Queirós et al. (2021) (70), administrative costing data from the University hospital Frankfurt am Main	COVID-19 ICU patients in Portugal

	Duration of mechanical ventilation[3]	10.76	10* base case: 1.08	Gamma	Ribeiro-Queirós et al. (2021) (70), administrative costing data from the University hospital Frankfurt am Main	COVID-19 ICU patients in Portugal
	In-hospital mortality	25%	0.07	Beta	Ribeiro-Queirós et al. (2021) (70)	COVID-19 ICU patients in Portugal
Life expectancy	Life expectancy female of age 63	23.7	NA	NA	OECD (2021) (60)	Portuguese general female population
	Life expectancy male of age 63	19.8	NA	NA	OECD (2021) (60)	Portuguese general male population
Utilities	Healthy stage 55-64 female[4A]	0.894	0.22	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 65-74 female[4A]	0.857	0.24	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 75+ female[4A]	0.729	0.35	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 55-64 male[4A]	0.909	0.24	Beta	Szende et al., 2014 (37)	Spanish general male population
	Healthy stage 65-74 male[4A]	0.936	0.14	Beta	Szende et al., 2014 (37)	Spanish general male population
	Healthy stage 75+ male[4A]	0.862	0.27	Beta	Szende et al., 2014 (37)	Spanish general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	18.87	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above

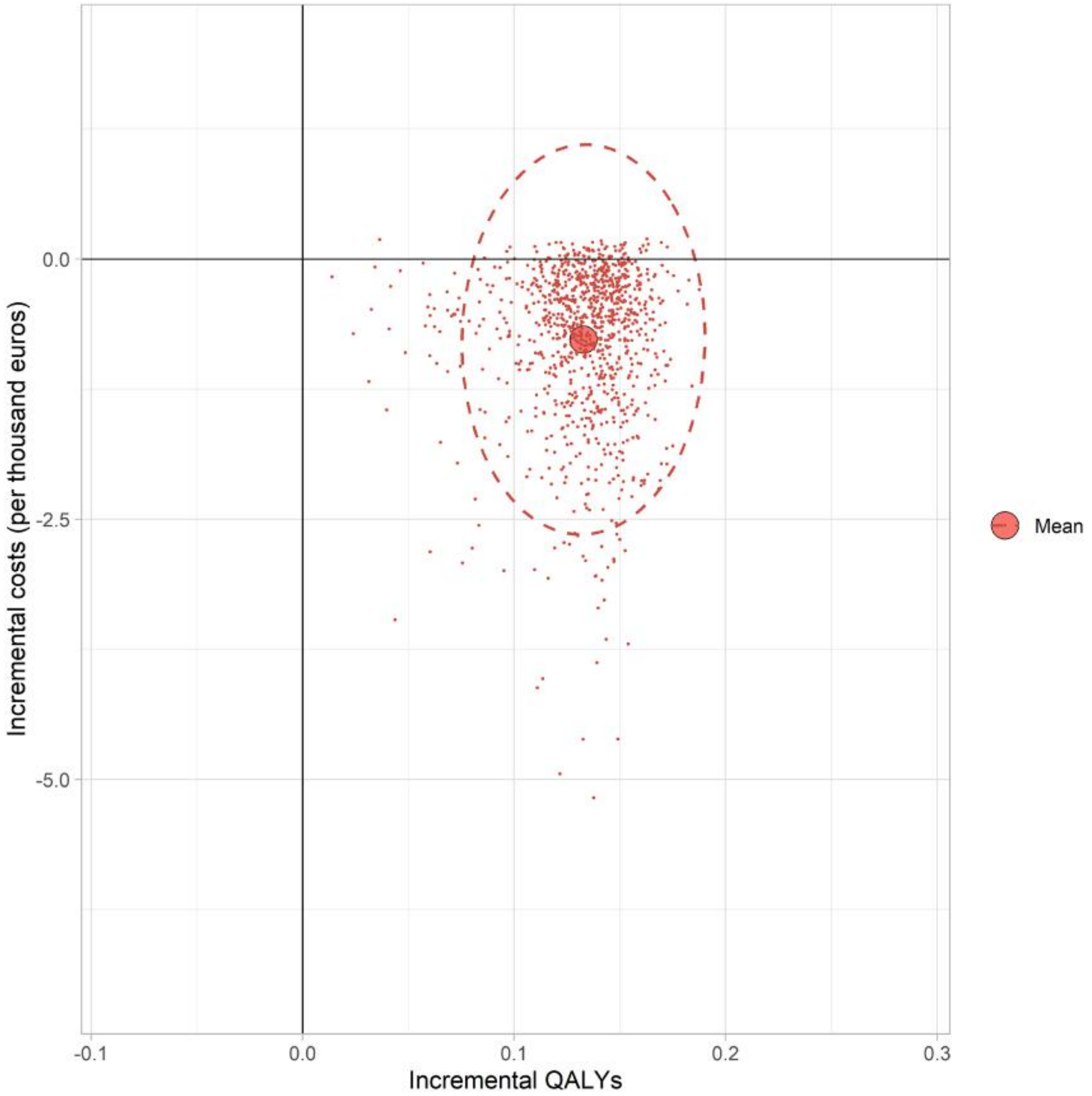
1. Daily Portuguese COVID-19 ICU occupancy in 2022 were obtained from European Centre for Disease Prevention and Control, 2022. Using the number of ICU beds in Portugal, that is 451 (67), we obtained the ICU occupancy, which was 30.24%. Taking into account that 88.6% of the ICU patients get mechanically ventilated (70) the estimated mechanically ventilated COVID-19 ICU occupancy in 2022 was: 26.79%.
2. Rounded to closest integer.
3. ICU LOS was taken from (70). To obtain the non-mechanical ventilation LOS and duration of mechanical ventilation, we used the German ratios.
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

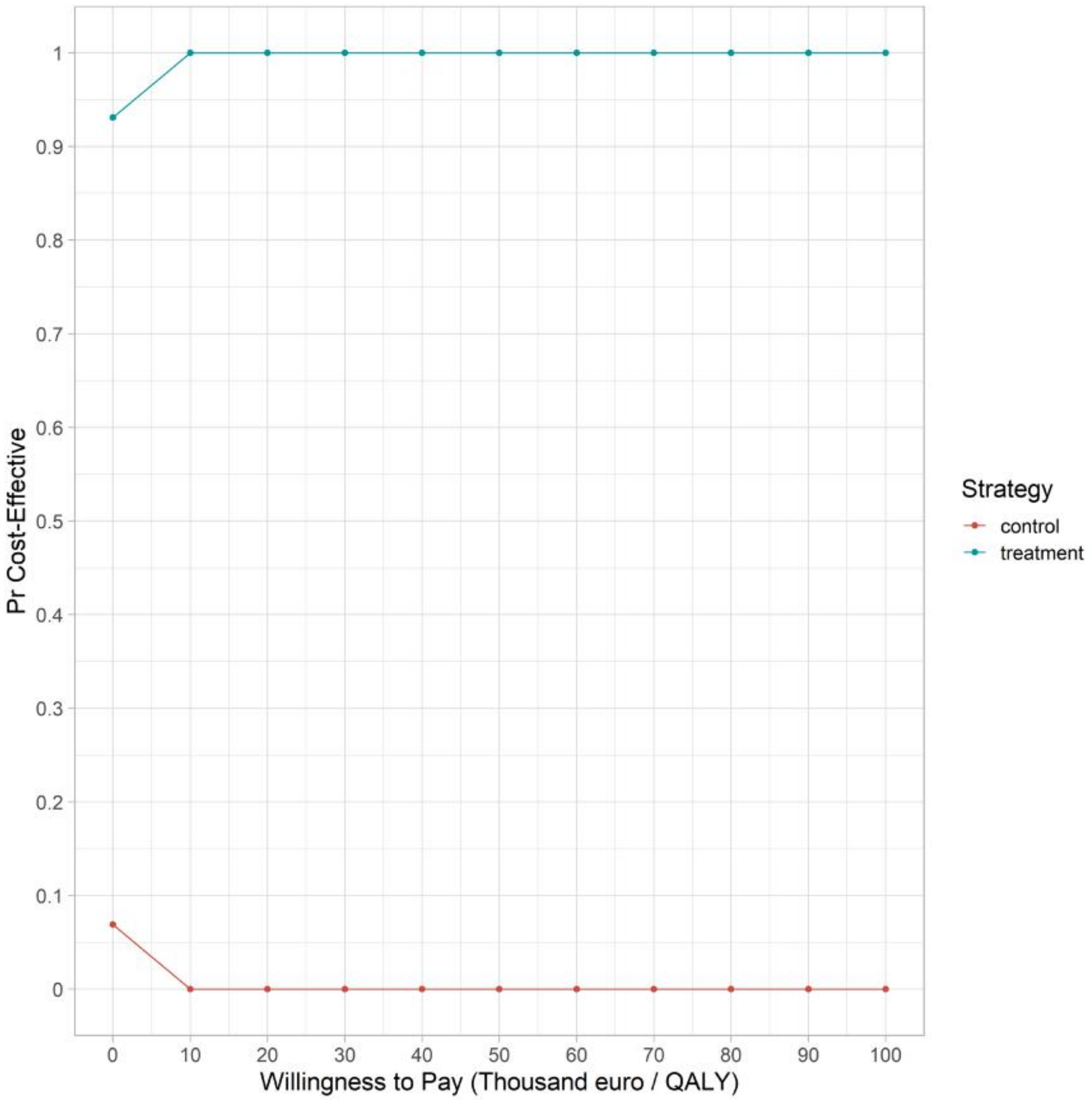
7.5.2 Results

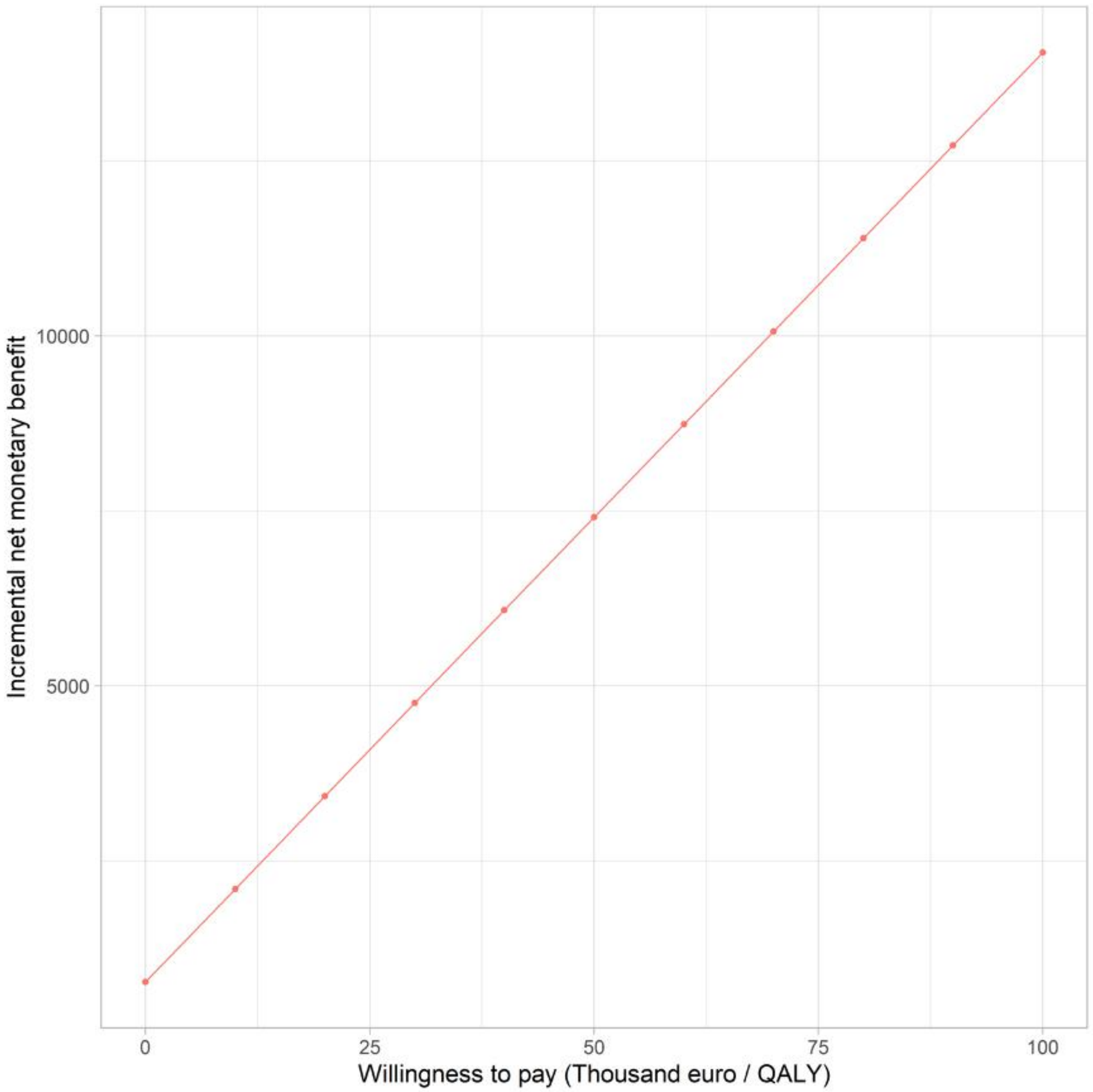
7.5.2.1 Results base case

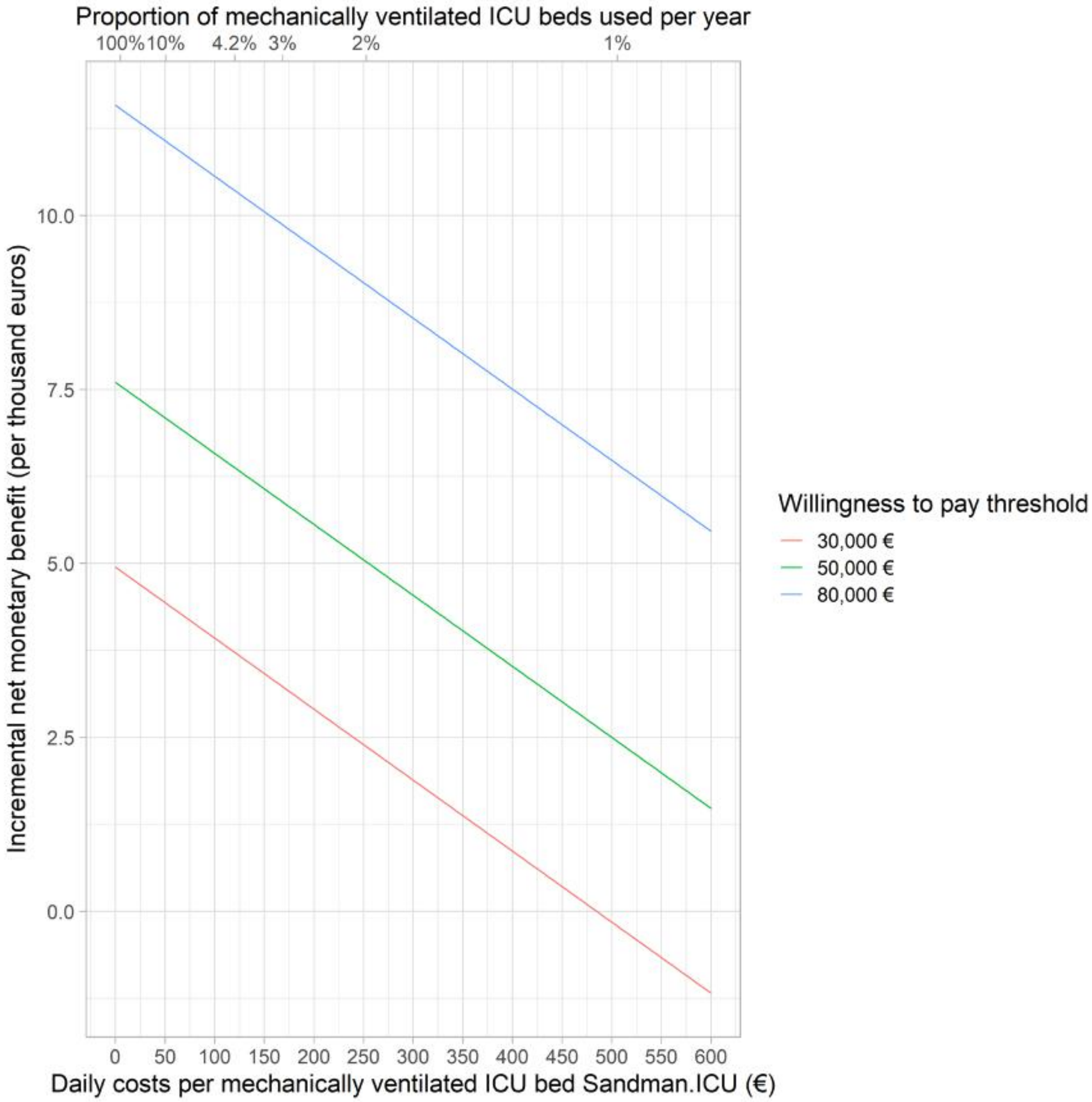
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	32,571.78	10.97	NA	NA	NA	NA
60	Treatment	31,781.02	11.12	-790.76	0.15	-5,384.41	7,763.66
63	Care as usual	32,571.78	9.98	NA	NA	NA	NA
63	Treatment	31,781.02	10.11	-790.76	0.13	-5,920.79	7,131.97
70	Care as usual	32,571.78	7.25	NA	NA	NA	NA
70	Treatment	31,781.02	7.35	-790.76	0.10	-8,133.20	5,407.03

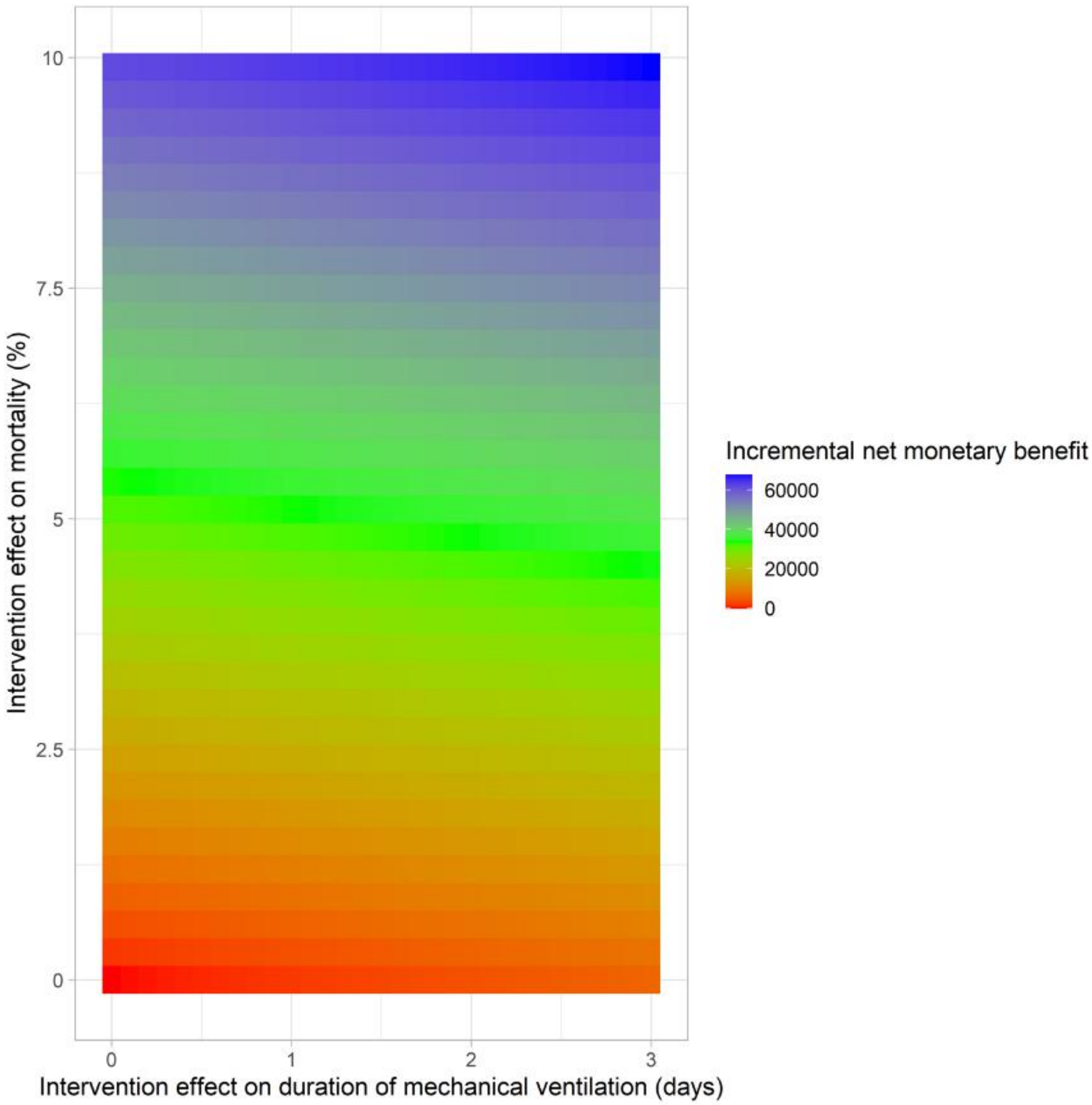
7.5.2.2 PSA results




Pr Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


Incremental net monetary benefit
10000
5000
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
10.0
7.5
5.0
2.5
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


10
7.5
5
2.5
0
Intervention effect on mortality (%)
0
1
2
3
Intervention effect on duration of mechanical ventilation (days)
Incremental net monetary benefit
60000
40000
20000
0

7.6 Romania

7.6.1 Parameters

Group of parameters	**Parameter**	**Base case (i.e. mean)**	**Standard deviation**	**Distribution probabilistic sensitivity analysis**	**Source**	**Studied population in source**
Country specific parameters	Willingness to pay	2*GDP per capita: 47,573.36	NA	NA	Serban et al. (2020) (71) The world bank (2021) (72) Eurostat (31)	NA
	Mechanical ventilated ICU occupancy[1]	8.2%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), Rhodes (2021)(67), Data from partner UMFCD	COVID-19 ICU patients in 2022 from Romania, Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
Population parameters	Age[2]	62	NA	NA	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
	Female	31.4%	NA	NA	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
In hospital parameters	Length of stay general ward	6.46	12.41	Gamma	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
	Length of stay ICU not mechanically ventilated	9.54	7.84	Gamma	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
	Duration of mechanical ventilation	4.69	7.53	Gamma	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania

	In-hospital mortality	48.57%	0.08	Beta	Data from partner UMFCD	Data on 35 COVID-19 patients admitted to ICU in UMFCD, Romania
Life expectancy	Life expectancy female of age 62	19.5	NA	NA	OECD (2021) (60)	Romanian general female population
	Life expectancy male of age 62	15.7	NA	NA	OECD (2021) (60)	Romanian general male population
Utilities	Healthy stage 55-64 female[4,5A]	0.724	0.24	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 65-74 female[4,5A]	0.687	0.26	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 75+ female[4,5A]	0.626	0.27	Beta	Szende et al., 2014 (37)	Hungarian general female population
	Healthy stage 55-64 male[4,5A]	0.798	0.24	Beta	Szende et al., 2014 (37)	Hungarian general male population
	Healthy stage 65-74 male[4,5A]	0.762	0.27	Beta	Szende et al., 2014 (37)	Hungarian general male population
	Healthy stage 75+ male[4,5A]	0.666	0.28	Beta	Szende et al., 2014 (37)	Hungarian general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	61.67	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above

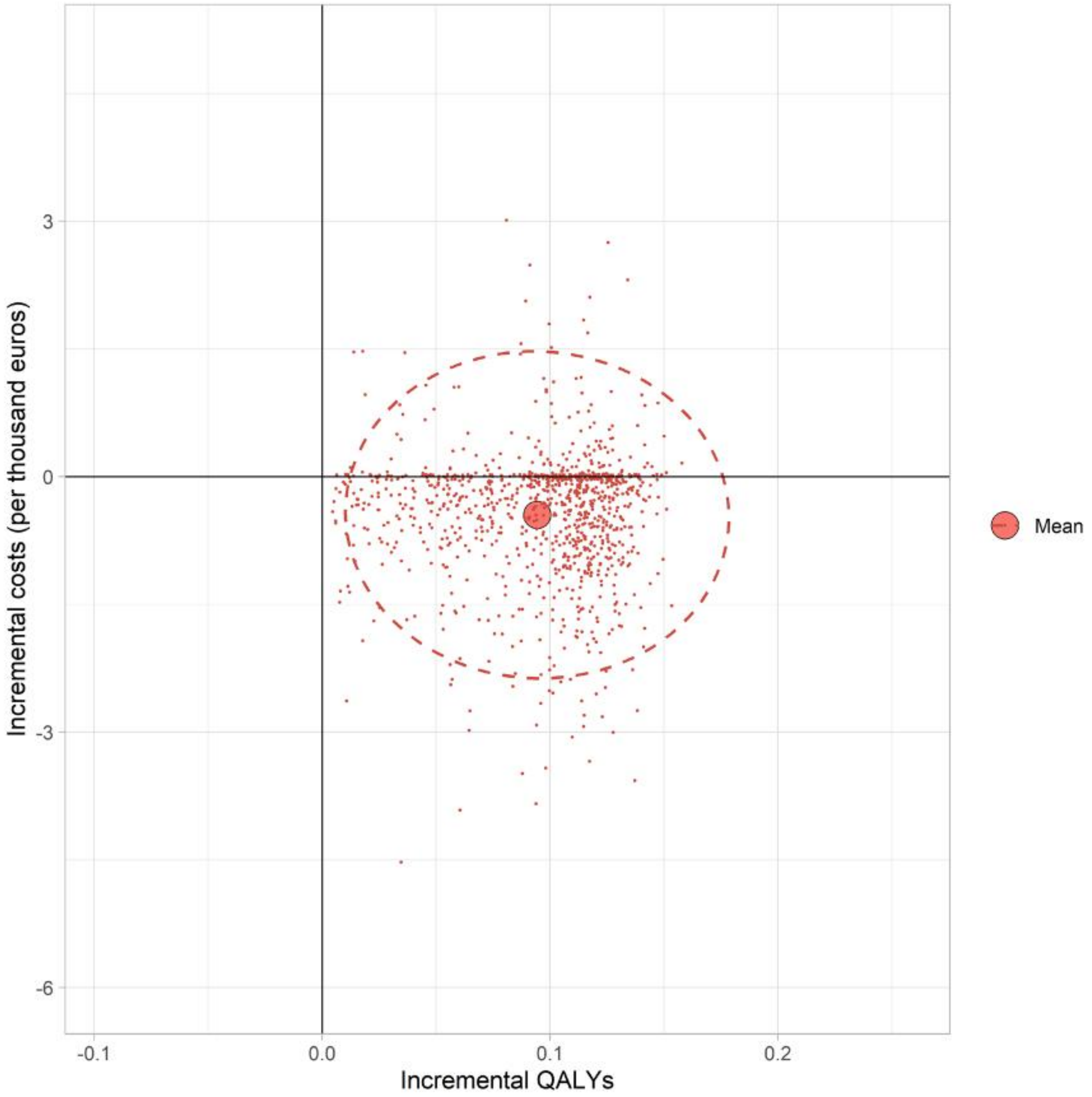
1. Weekly ICU occupancy in Romania was obtained from European Centre for Disease Prevention and Control, 2022 (29), which was on average 286.15 occupied ICU beds. This was divided by the number of ICU beds available: 2000 (67). Subsequently we multiplied this with the proportion of mechanically ventilated ICU patients (data from UMFCD)
2. Rounded to nearest integer.
3. Taken with EQ-5D index value (European VAS value set).
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

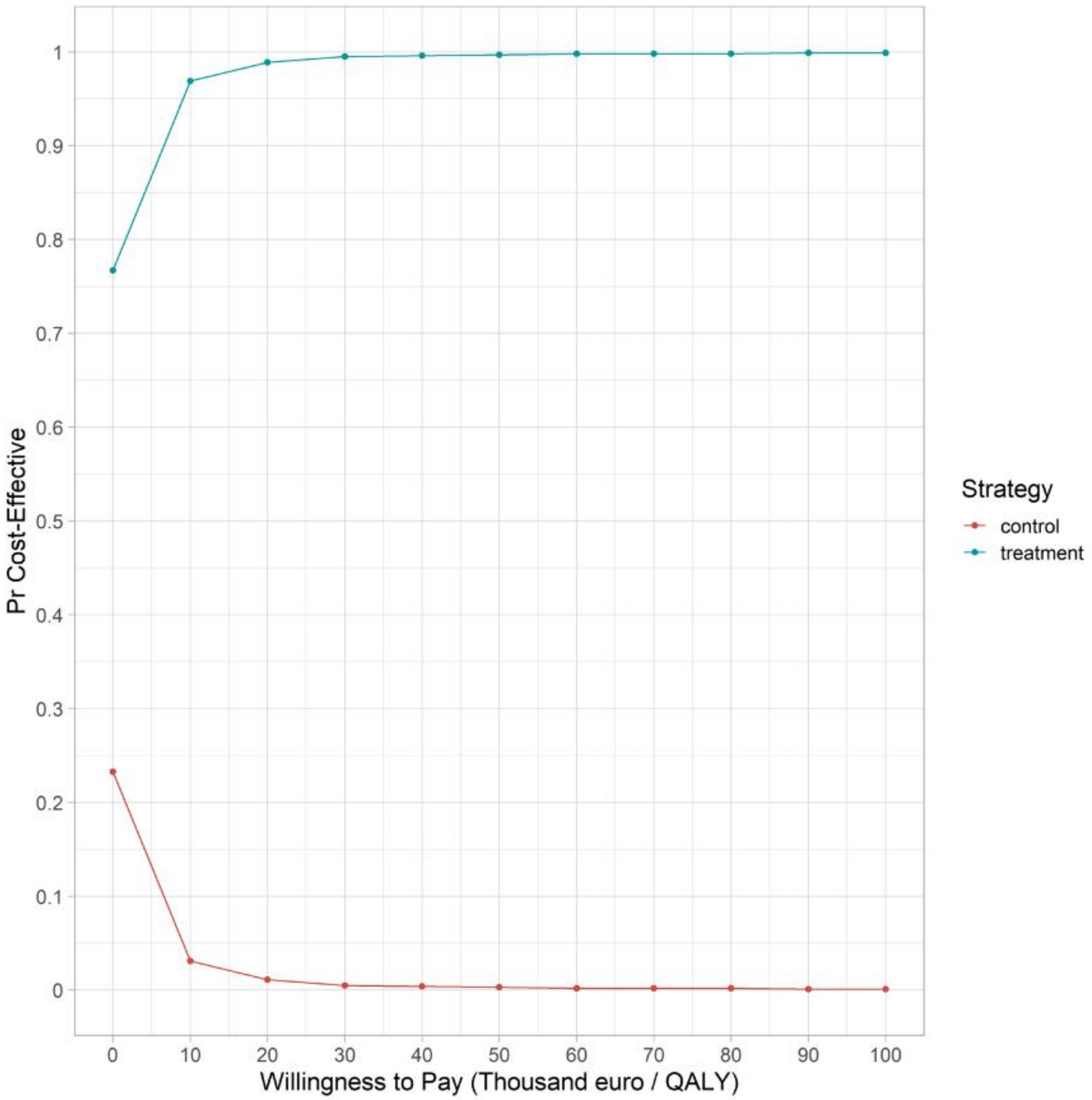
7.6.2 Results

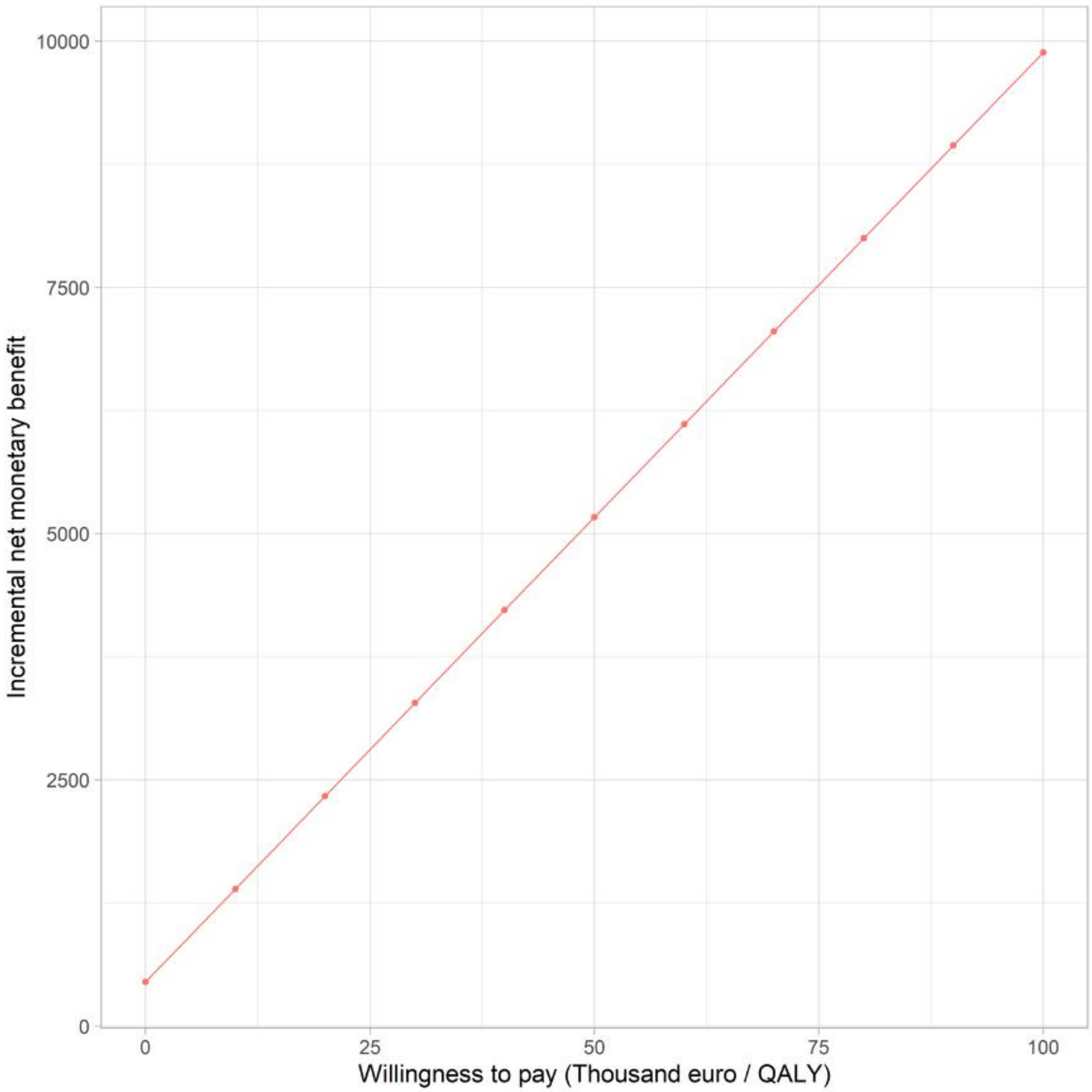
7.6.2.1 Results base case

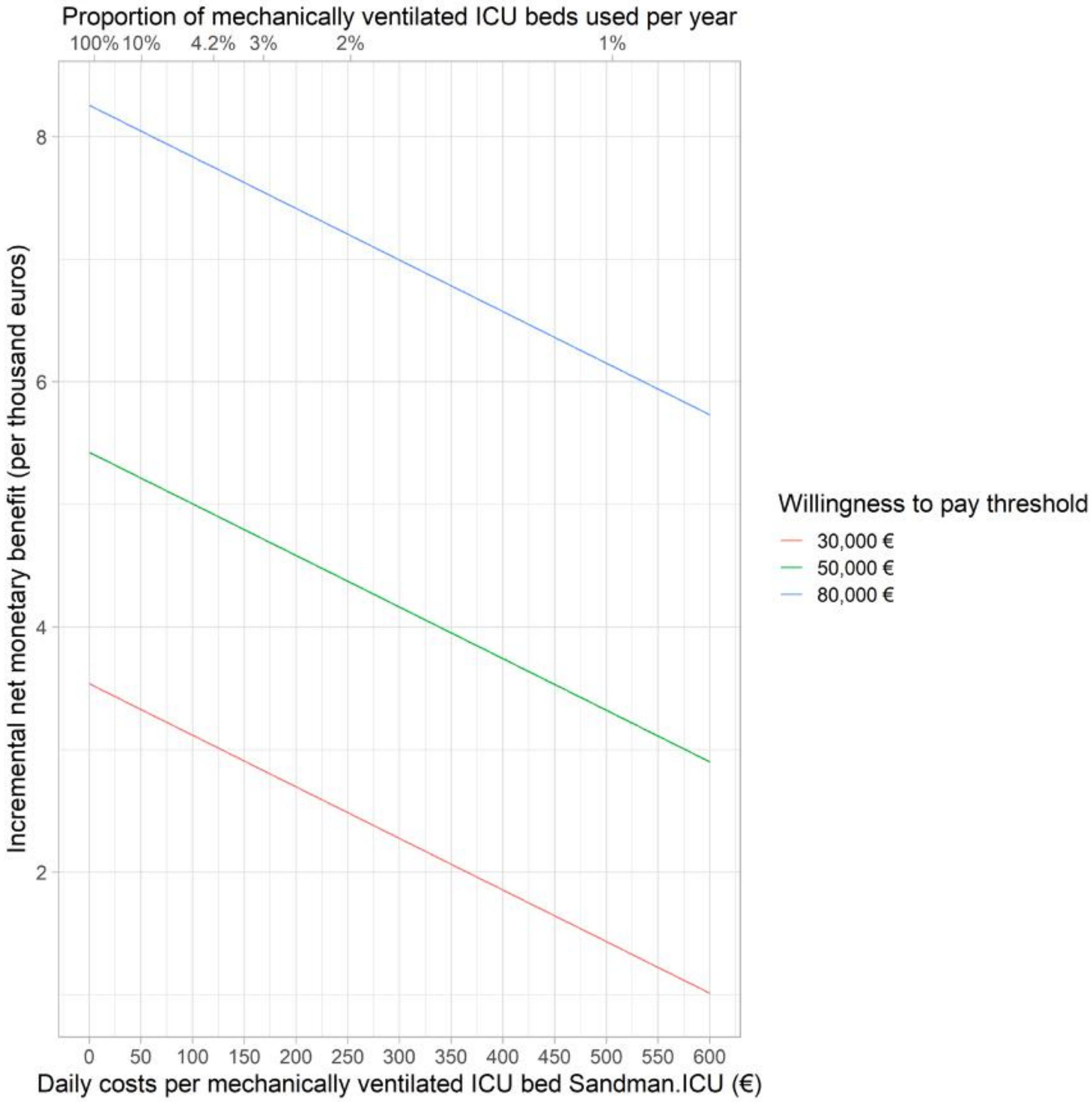
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
62	Care as usual	20,725.90	4.90	NA	NA	NA	NA
62	Treatment	19,999.61	4.99	-726.29	0.10	-7,584.74	5,281.78
65	Care as usual	20,725.90	4.17	NA	NA	NA	NA
65	Treatment	19,999.61	4.25	-726.29	0.08	-8,886.91	4,614.28
70	Care as usual	20,725.90	2.89	NA	NA	NA	NA
70	Treatment	19,999.61	2.95	-726.29	0.06	-12,777.78	3,430.38

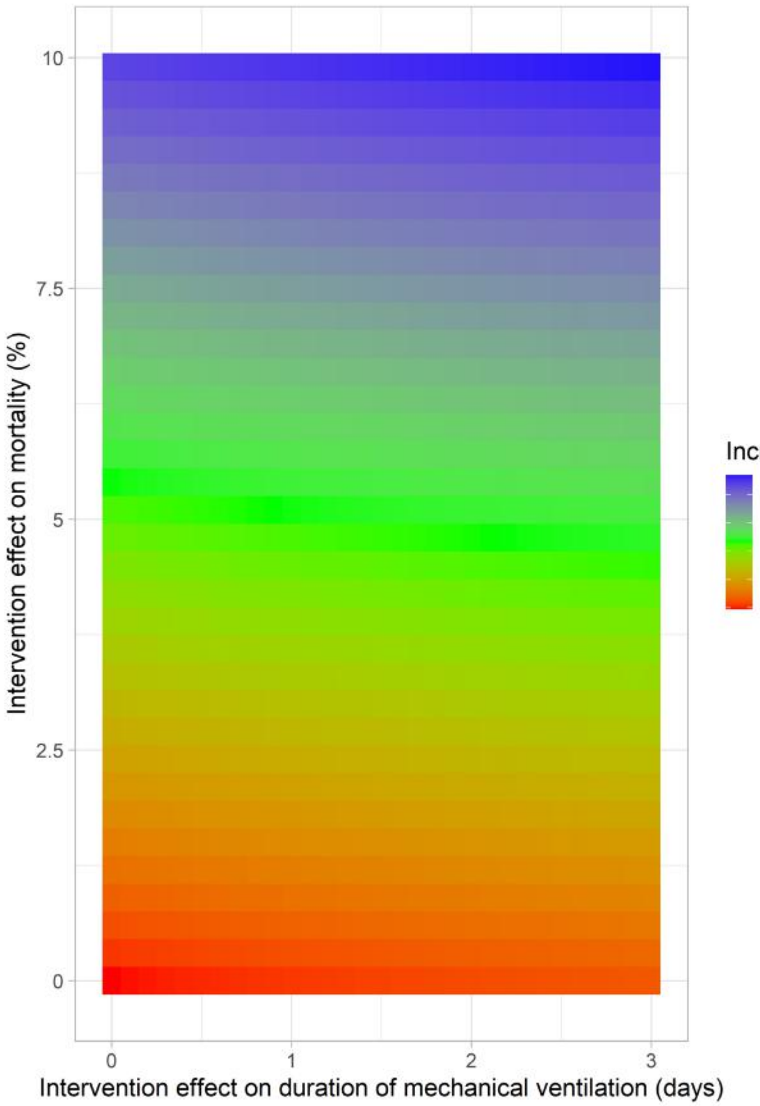
7.6.2.2 PSA results




Pr Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


10000
7500
5000
2500
0
Incremental net monetary benefit
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
8
6
4
2
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


10
7.5
5
2.5
0
Intervention effect on mortality (%)
0
1
2
3
Intervention effect on duration of mechanical ventilation (days)
Incremental net monetary benefit
40000
30000
20000
10000
0

7.7 Slovenia

7.7.1 Parameters

Group of parameters	Parameter	Base case (i.e. mean)	Standard deviation	Distribution probabilistic sensitivity analysis	Source	Studied population in source
Country specific parameters	Willingness to pay	29,429.63	NA	NA	Kovács et al. (2022) (55) Eurostat (31)	NA
	Mechanical ventilated ICU occupancy[1]	7.1%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), Muzlovič et al. (2020) (73), Benes et al., 2022 (59)	ICU COVID-19 patients in Slovenia and mechanical ventilated COVID-19 patients in eastern Europe
Population parameters	Age[2]	66	NA	NA	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia
	Female	45.7%	NA	NA	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia
In hospital parameters	Length of stay general ward	14.49	15.59	Gamma	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia
	Length of stay ICU not mechanically ventilated	7.93	9.62	Gamma	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia
	Duration of mechanical ventilation	18.93	13.38	Gamma	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia

	In-hospital mortality	62.86%	0.08	Beta	Data from ICU COVID-19 patients UMCM	35 ICU COVID-19 patients admitted to UMCM, Slovenia
Life expectancy	Life expectancy female of age 66	20.3	NA	NA	OECD (2021) (60)	Slovenian general population
	Life expectancy male of age 66	16.2	NA	NA	OECD (2021) (60)	Slovenian general population
Utilities	Healthy stage 65-74 female[3,4A]	0.630	0.22	Beta	Szende et al., 2014 (37)	Slovenian general female population
	Healthy stage 75+ female[3,4A]	0.600	0.17	Beta	Szende et al., 2014 (37)	Slovenian general female population
	Healthy stage 65-74 male[3,4A]	0.701	0.16	Beta	Szende et al., 2014 (37)	Slovenian general male population
	Healthy stage 75+ male[3,4A]	0.663	0.18	Beta	Szende et al., 2014 (37)	Slovenian general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	71.23	NA	NA	See section 2.4.1, Eurostat (31), OECD (34)	Calculated using ICU occupancy above
	General ward per day[4B]	462.63	10%*base case: 46.26	Gamma	Internal communication UMCM	COVID-19 patients without complications
	ICU not mechanically ventilated per day[4B]	682.77	10%* base case: 68.28	Gamma	Internal communication UMCM	COVID-19 patients with complications
	Mechanically ventilated per day[4B]	1273.71	10%*base case: 127.37	Gamma	Internal communication UMCM	Mechanically ventilated COVID-19 patients

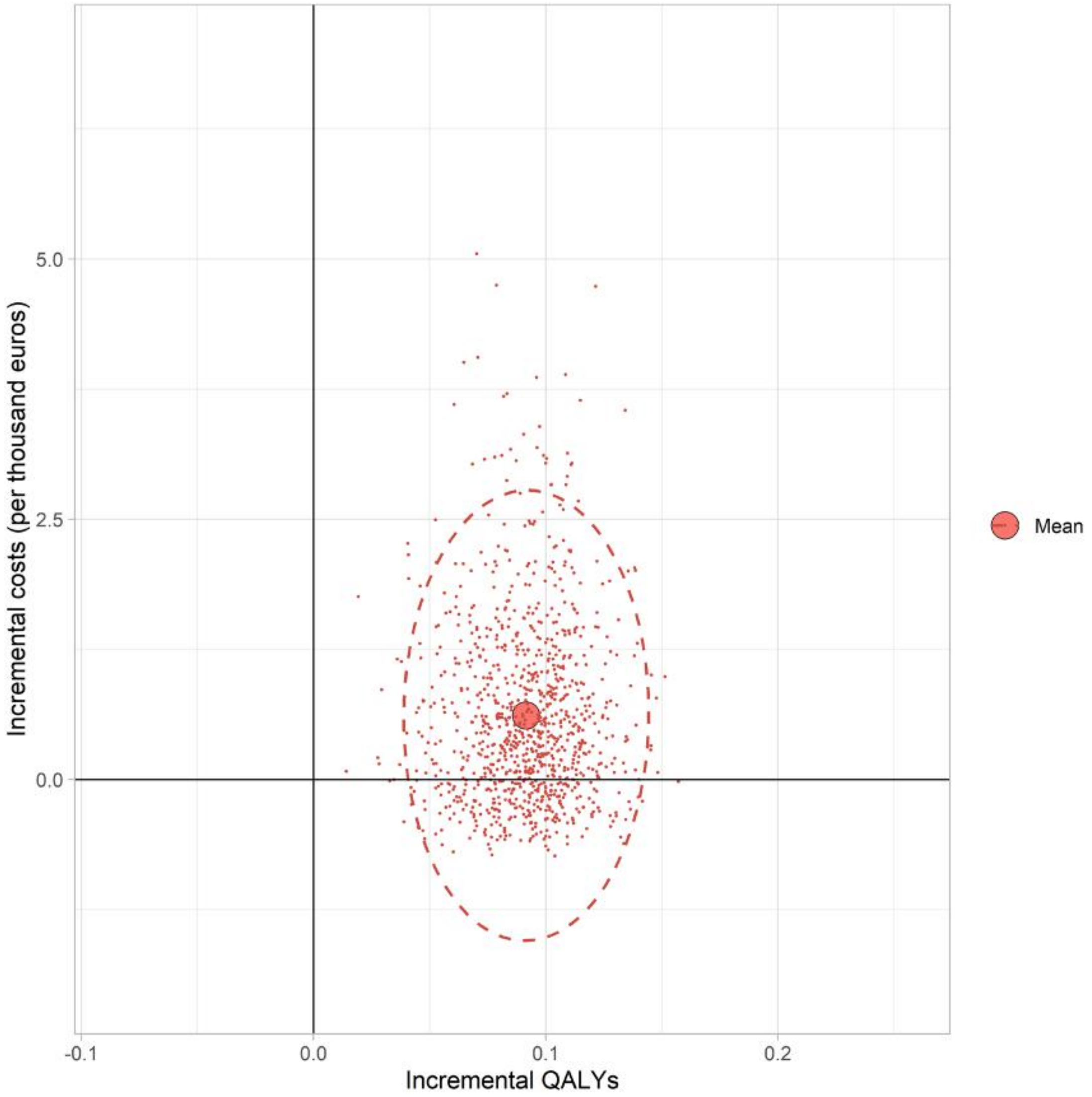
1. Weekly ICU occupancy in Slovenia was obtained from European Centre for Disease Prevention and Control, 2022 (29), which was on average 41.27 occupied ICU beds. This was divided by the number of ICU beds: 290 (73). Subsequently this was multiplied with the proportion of mechanically ventilated ICU patients (59)
2. Rounded to the nearest integer.
3. Taken with EQ-5D index value (European VAS value set).
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

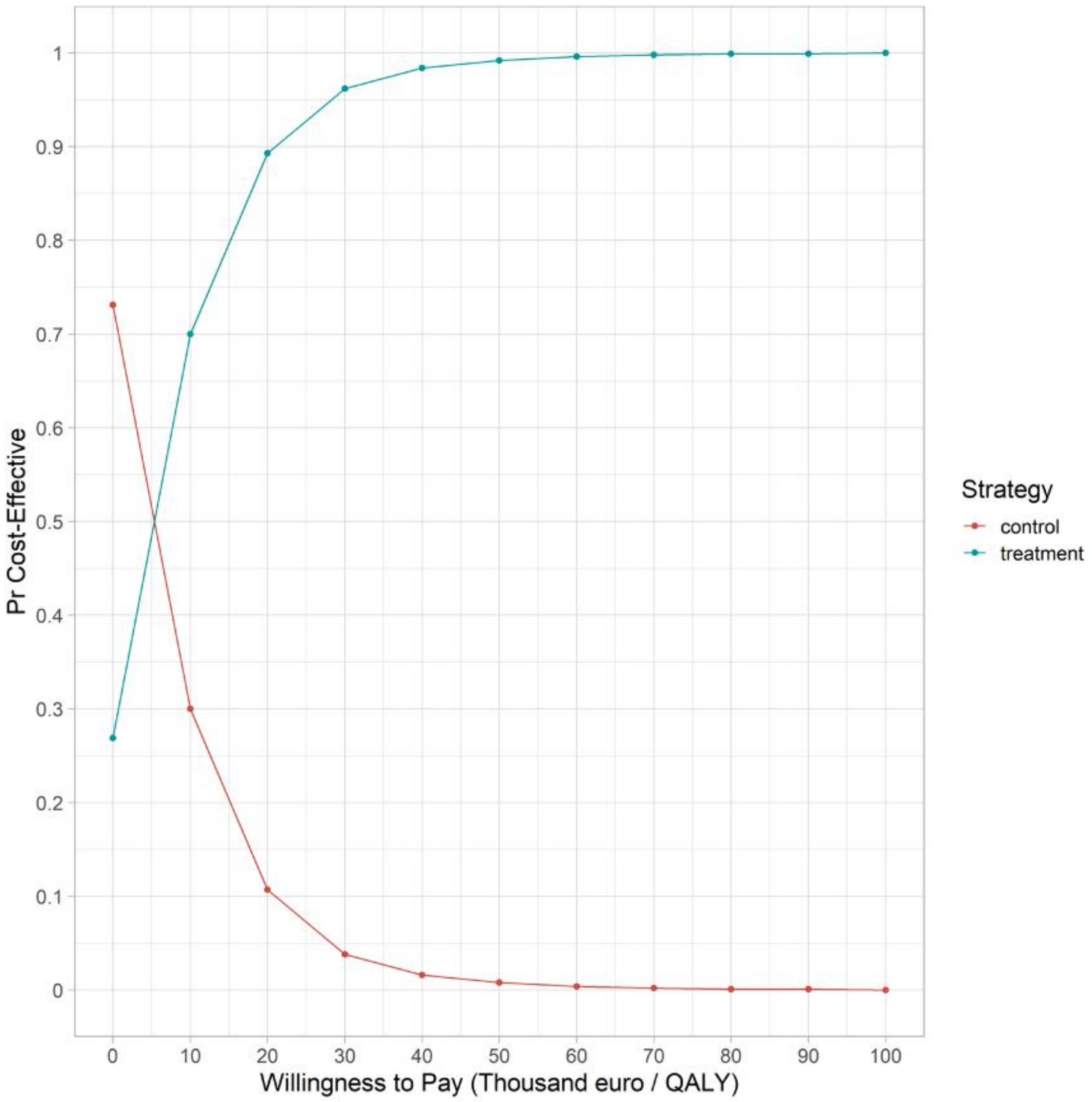
7.7.3 Results

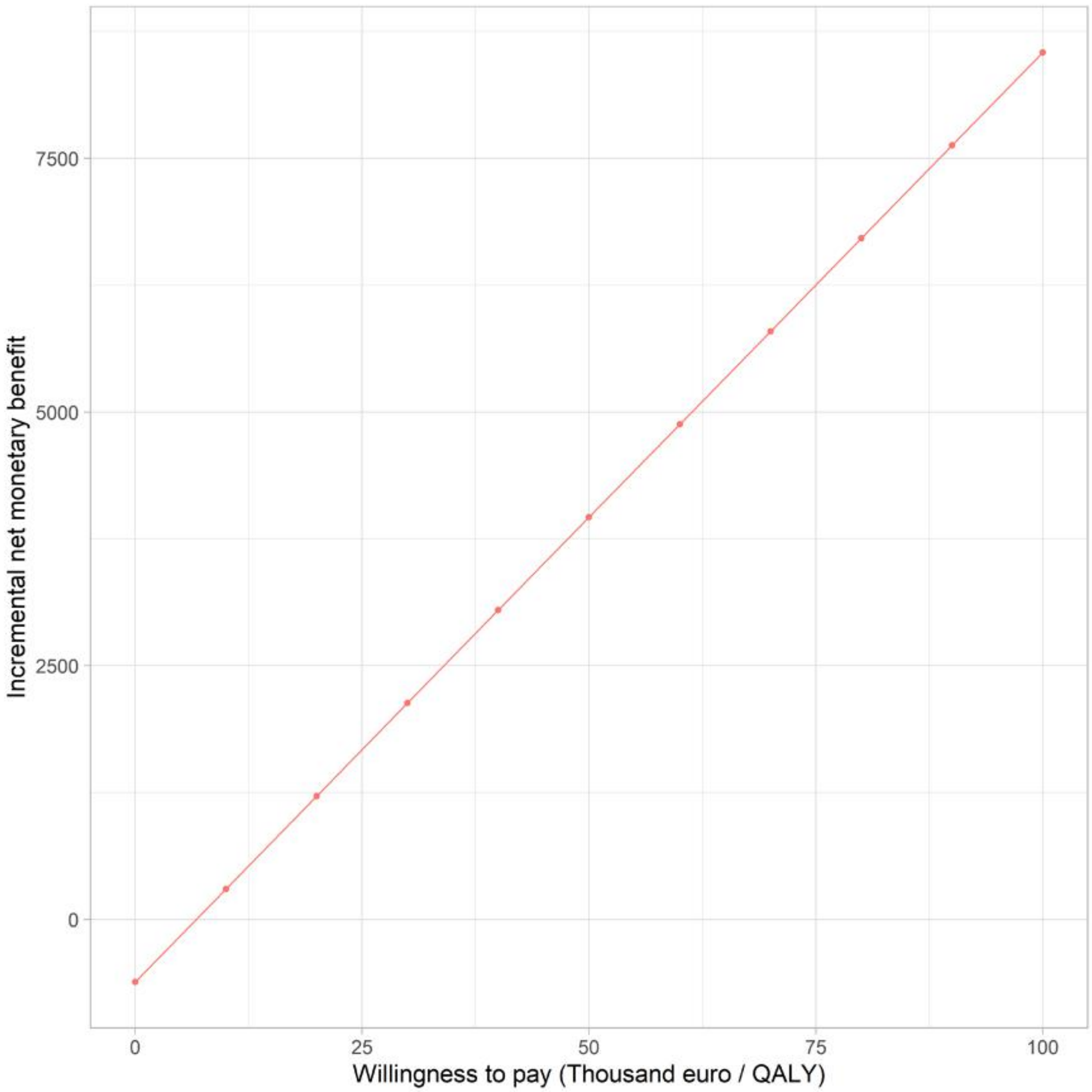
7.7.3.1 Results base case

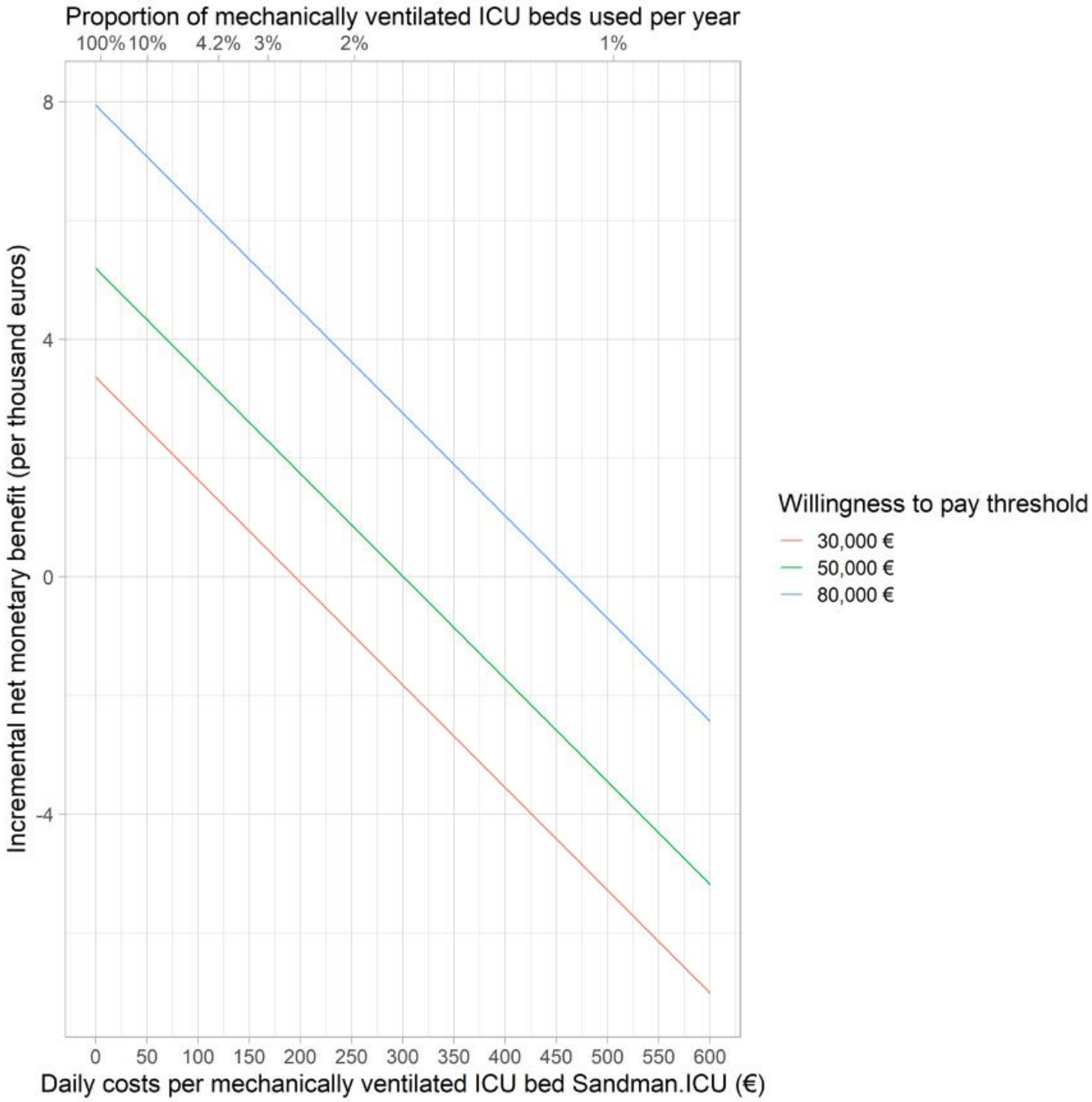
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
60	Care as usual	37,027.04	4.12	NA	NA	NA	NA
60	Treatment	37,723.23	4.23	696.19	0.11	6,248.78	2,582.62
66	Care as usual	37,027.04	3.32	NA	NA	NA	NA
66	Treatment	37,723.23	3.41	696.19	0.09	7,738.58	1,951.39
70	Care as usual	37,027.04	2.73	NA	NA	NA	NA
70	Treatment	37,723.23	2.81	696.19	0.07	9,377.18	1,488.75

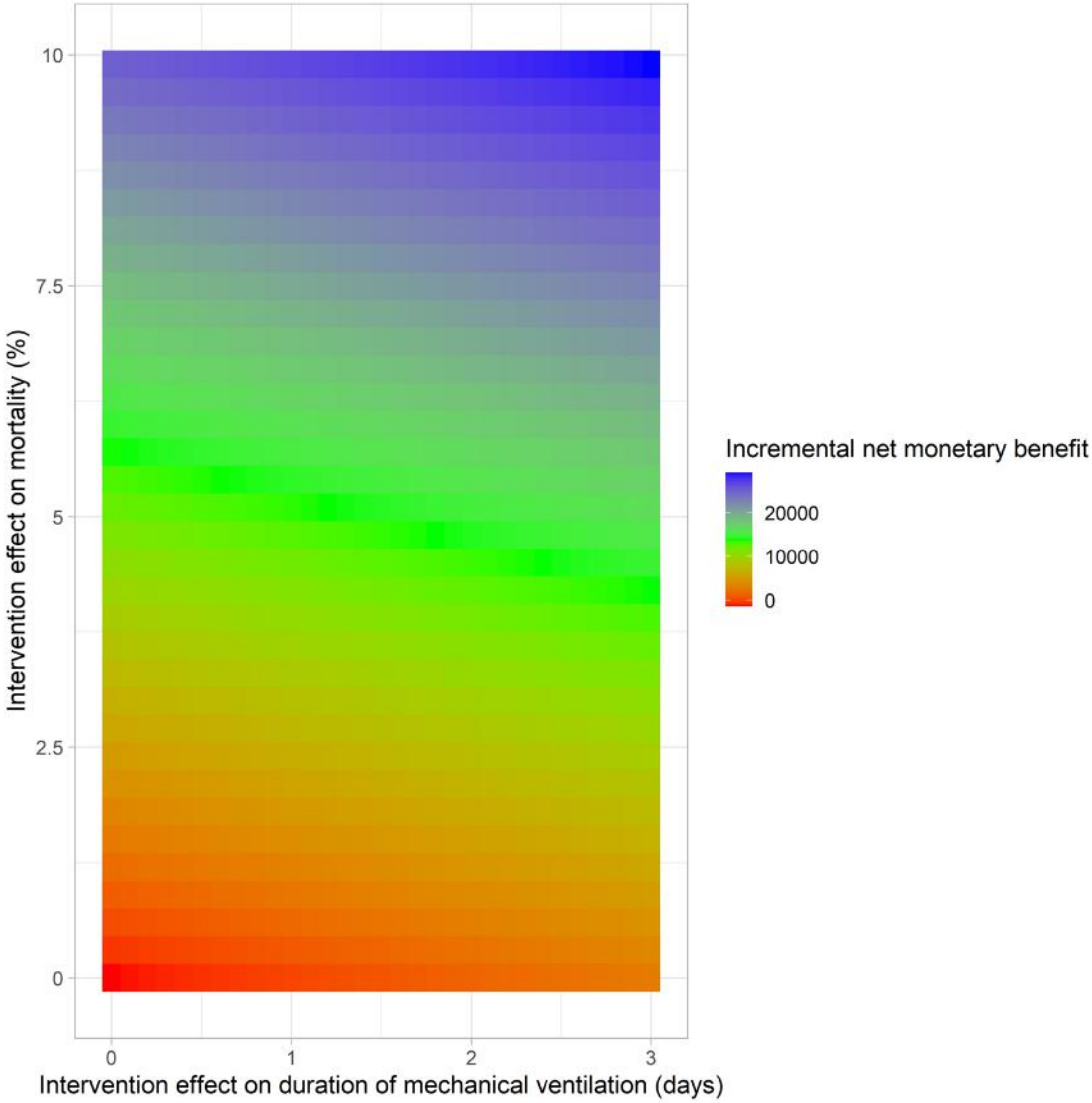
7.7.3.2 PSA results




Pr Cost-Effective
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


Incremental net monetary benefit
7500
5000
2500
0
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
8
4
0
-4
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


Intervention effect on mortality (%)
10
7.5
5
2.5
0
Intervention effect on duration of mechanical ventilation (days)
0
1
2
3
Incremental net monetary benefit
20000
10000
0

7.8 Spain

7.8.1 Parameters

Group of parameters	**Parameter**	**Base case (i.e. mean)**	**Standard deviation**	**Distribution probabilistic sensitivity analysis**	**Source**	**Studied population in source**
Country specific parameters	Willingness to pay	26,478.82	NA	NA	Sacristán et al. (2020)(74)	NA
	Mechanical ventilated ICU occupancy[1]	11.3%	NA	NA	European Centre for Disease Prevention and Control, 2022 (29), OECD (2020) The world bank (2021), Rodriguez-Gonzalez (2021) (75)	COVID-19 ICU patients in Spain
Population parameters	Age[2]	62	NA	NA	Data ICU COVID-19 patients of partner ICS-HUB	503 ICU COVID-19 patients of partner ICS-HUB, Spain
	Female	26.24%	NA	NA	Data ICU COVID-19 patients of partner ICS-HUB	503 ICU COVID-19 patients of partner ICS-HUB, Spain
In hospital parameters	Length of stay general ward	14.06	19.54	Gamma	Data ICU COVID-19 patients of partner ICS-HUB	503 ICU COVID-19 patients of partner ICS-HUB, Spain

	Length of stay ICU not mechanically ventilated[3]	7.26	10*base case: 0.73	Gamma	Data ICU COVID-19 patients of partner ICS-HUB, administrative costing data from the University hospital Frankfurt am Main	503 ICU COVID-19 patients of partner ICS-HUB, Spain, German mechanically ventilated COVID-19 patients
	Duration of mechanical ventilation[3]	15.22	10* base case: 1.52	Gamma	Data ICU COVID-19 patients of partner ICS-HUB, administrative costing data from the University hospital Frankfurt am Main	503 ICU COVID-19 patients of partner ICS-HUB, Spain, German mechanically ventilated COVID-19 patients
	In-hospital mortality	44.73%	0.02	Beta	Data ICU COVID-19 patients of partner ICS-HUB	503 ICU COVID-19 patients of partner ICS-HUB, Spain
Life expectancy	Life expectancy female of age 62	26.5	NA	NA	OECD (2021) (60)	Spanish general female population
	Life expectancy male of age 62	22.1	NA	NA	OECD (2021) (60)	Spanish general male population
Utilities	Healthy stage 55-64 female[4A]	0.894	0.22	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 65-74 female[4A]	0.857	0.24	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 75+ female[4A]	0.729	0.35	Beta	Szende et al., 2014 (37)	Spanish general female population
	Healthy stage 55-64 male[4A]	0.909	0.24	Beta	Szende et al., 2014 (37)	Spanish general male population

	Healthy stage 65-74 male[4A]	0.936	0.14	Beta	Szende et al., 2014 (37)	Spanish general male population
	Healthy stage 75+ male[4A]	0.862	0.27	Beta	Szende et al., 2014 (37)	Spanish general male population
Costs	Treatment costs for Sandman.ICU per mechanically ventilated bed day	44.75	NA	NA	See section 2.4.1, Eurostat (31)	Calculated using ICU occupancy above
	General ward per day[4B]	549.48	10%* base case: 55.45	Gamma	Data from partner ICS-HUB, Eurostat (31,38)	503 Spanish COVID-19 ICU patients

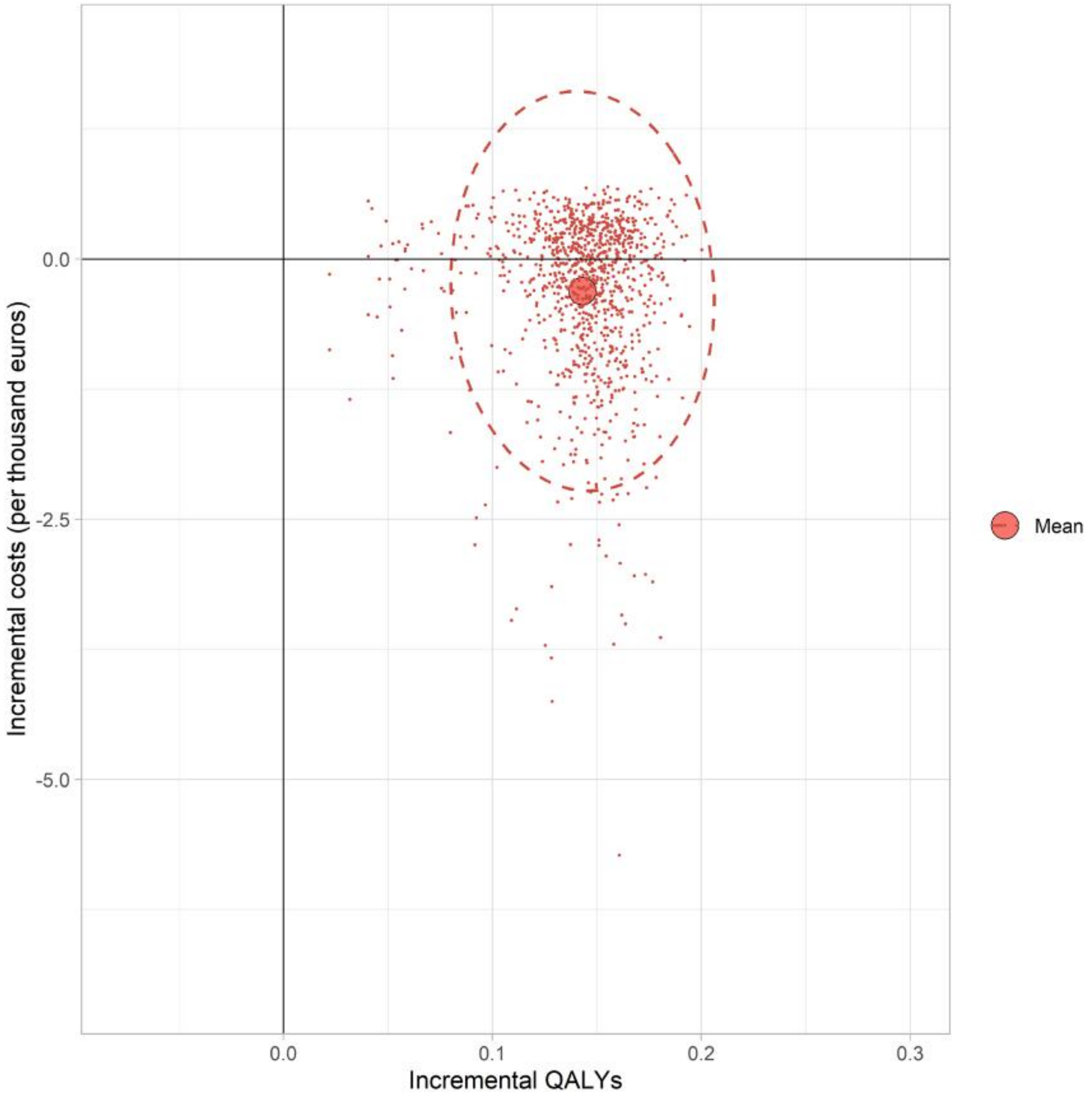
1. Number of weekly Spanish COVID-19 ICU occupancy in 2022 were obtained from European Centre for Disease Prevention and Control, 2022. In Spain there are 9.7 ICU beds per 100,000 inhabitants (46). Taking into account the number of inhabitants in Spain (76), we obtained the ICU occupancy, which was 12.57%. Taking into account that 89.68% of the ICU patients get mechanically ventilated (75) the estimated mechanically ventilated COVID-19 ICU occupancy in 2022 was: 11.3%.
2. Rounded to the nearest integer.
3. ICU LOS was estimated using the Spanish data set. To obtain the non-mechanical ventilation LOS and duration of mechanical ventilation, we used the German ratios.
4. In the PSA ratios were kept fixed between these variables (grouped with letters).

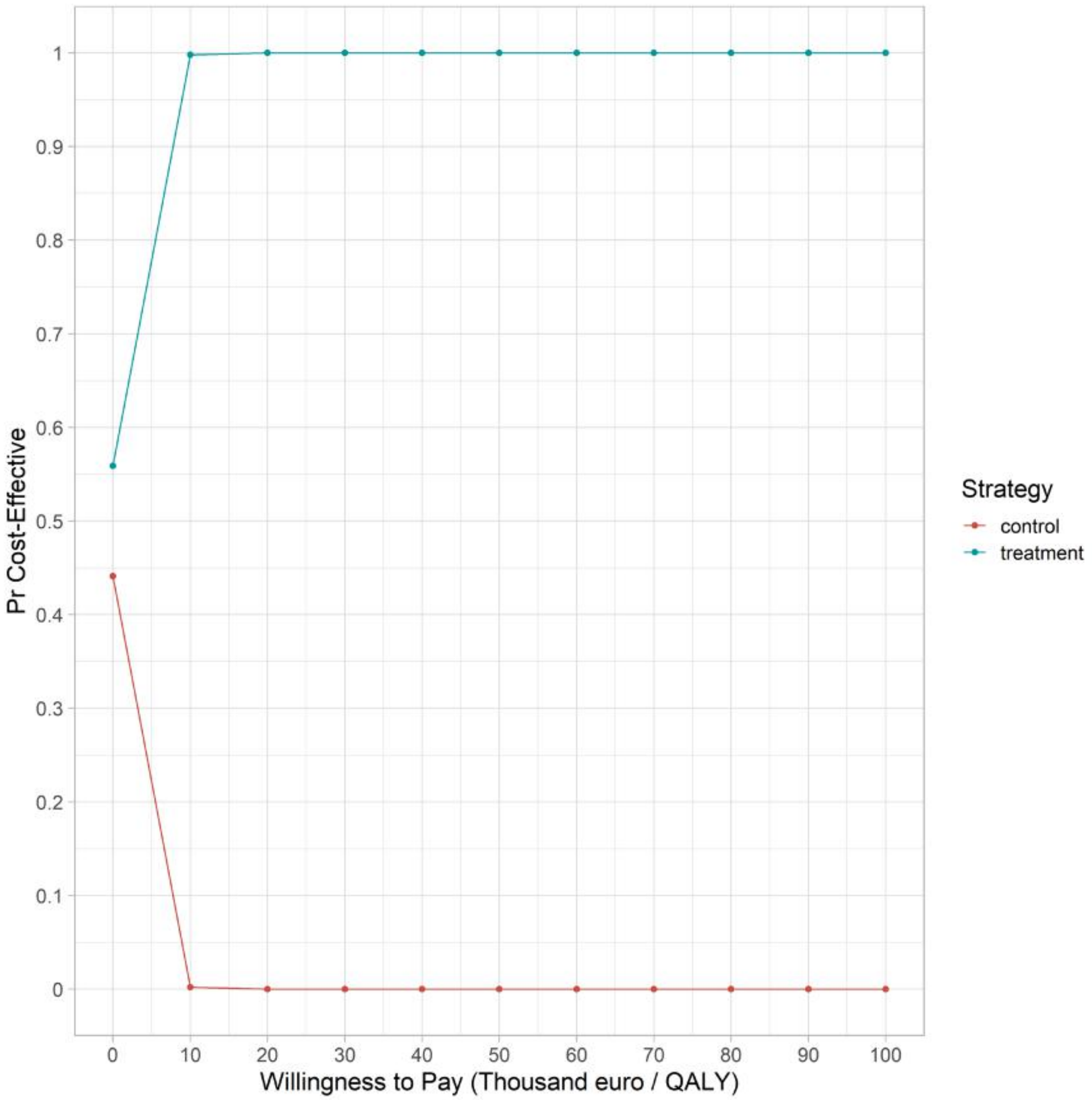
7.8.3 Results

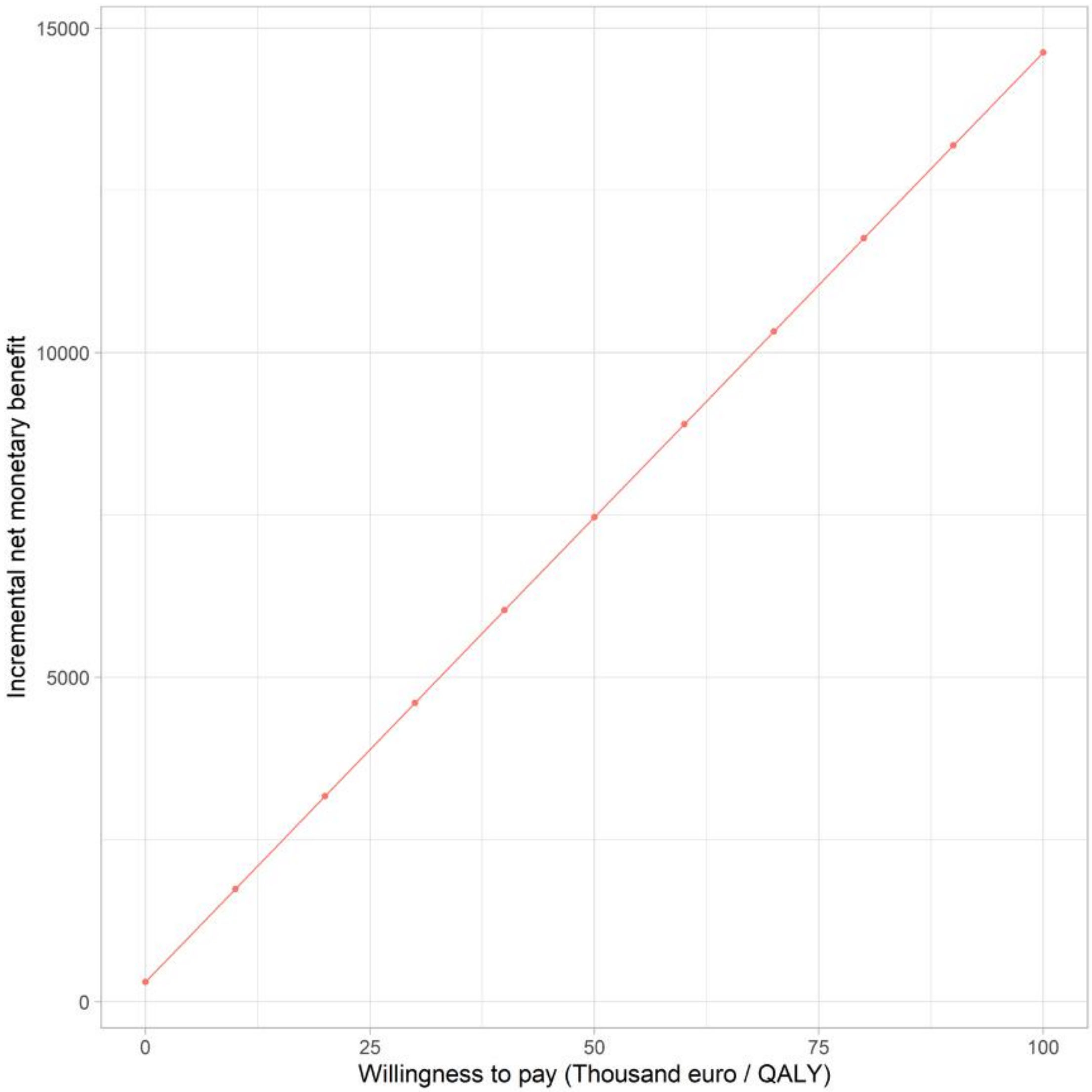
7.8.3.1 Results base case

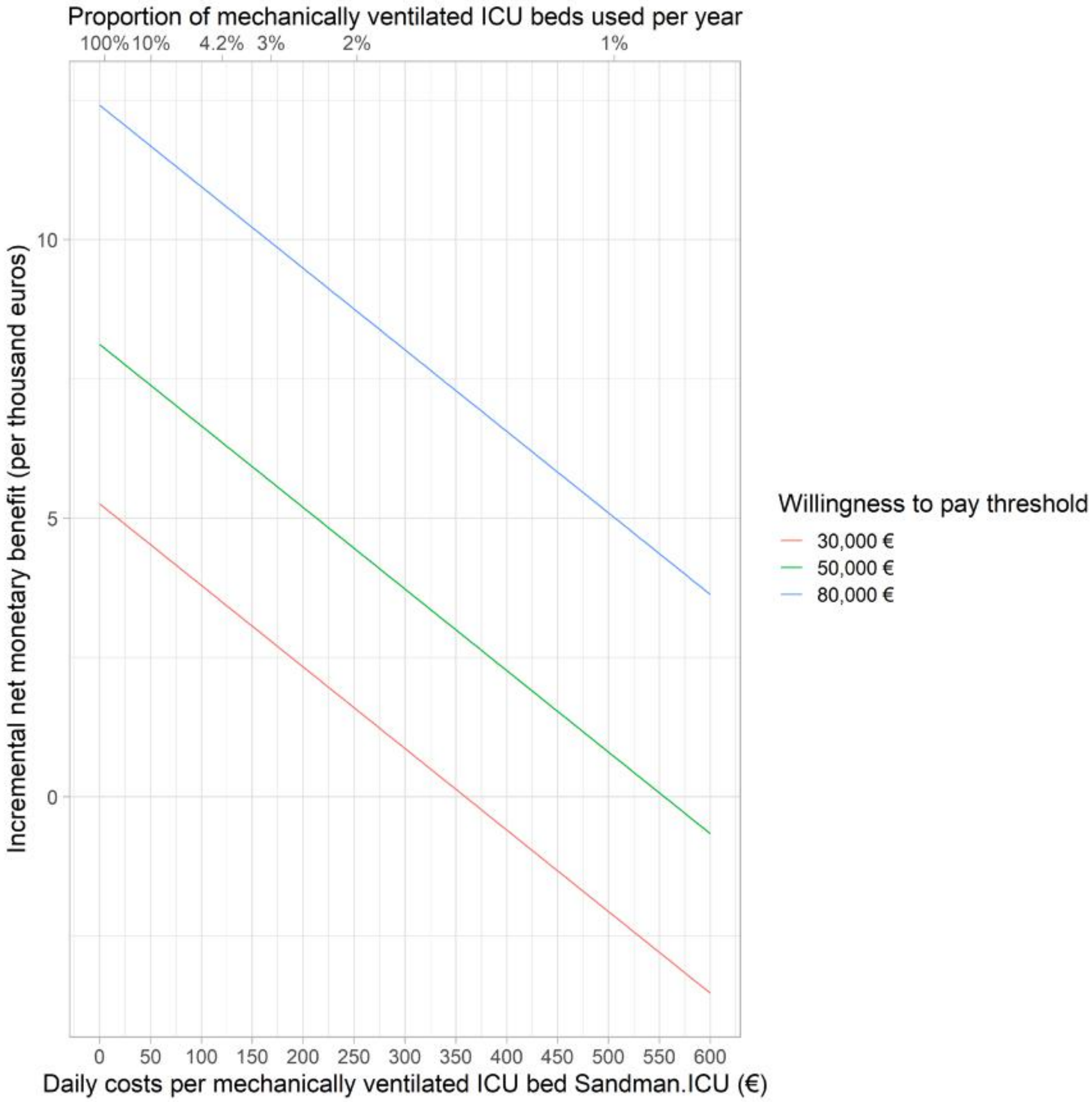
Age assumed	Care provided	Costs	QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio (€/QALY)	Incremental net monetary benefit (€)
62	Care as usual	45,421.69	7.91	NA	NA	NA	NA
62	Treatment	45,097.63	8.05	-324.06	0.14	-2,262.87	4,116.08
65	Care as usual	45,421.69	7.15	NA	NA	NA	NA
65	Treatment	45,097.63	7.28	-324.06	0.13	-2,502.27	3,753.30
70	Care as usual	45,421.69	5.71	NA	NA	NA	NA
70	Treatment	45,097.63	5.81	-324.06	0.10	-3,134.54	3,061.58

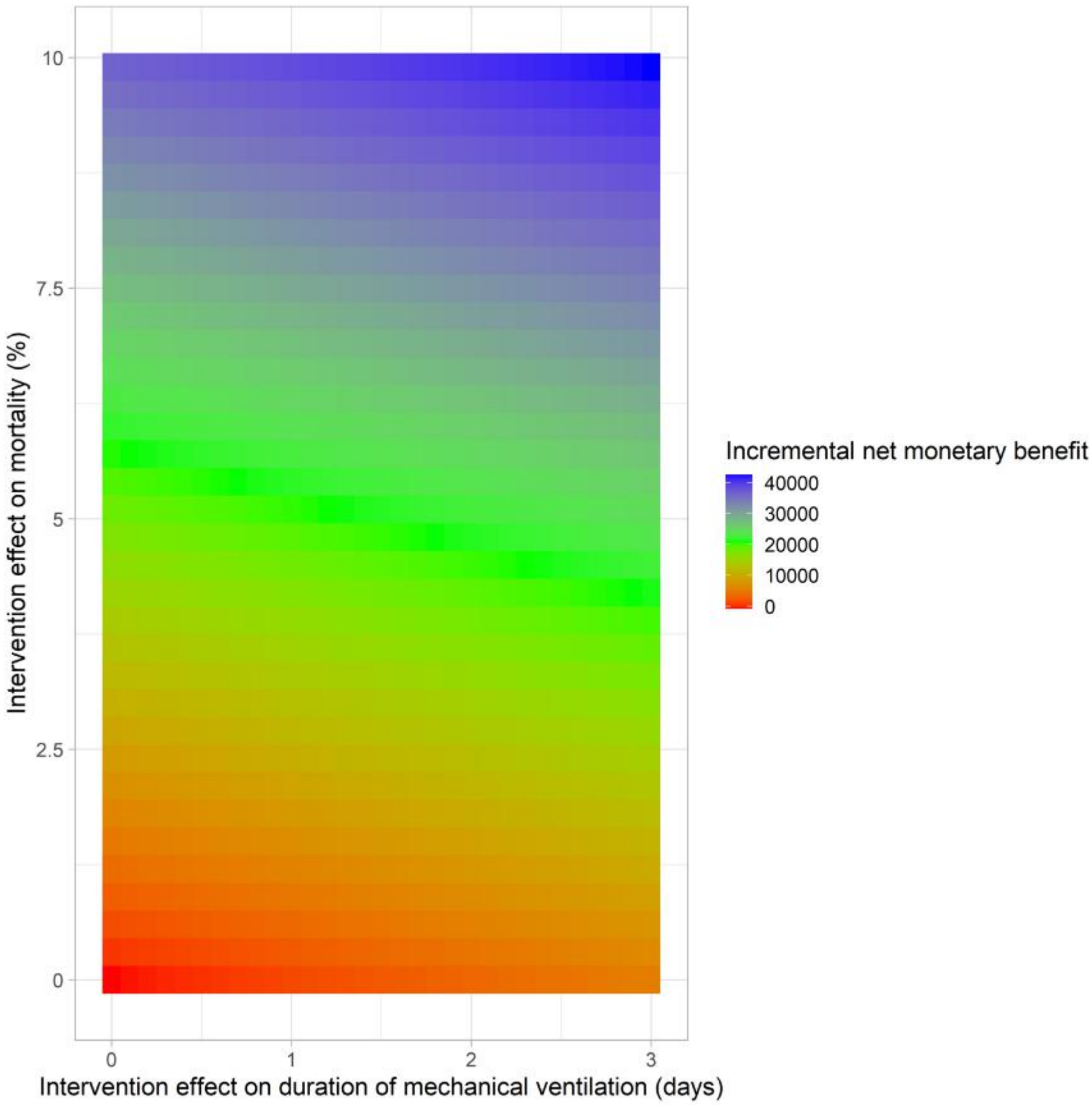
7.8.3.2 PSA results




Pr Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
60
70
80
90
100
Willingness to Pay (Thousand euro / QALY)
Strategy
control
treatment


15000
10000
5000
0
Incremental net monetary benefit
0
25
50
75
100
Willingness to pay (Thousand euro / QALY)


Proportion of mechanically ventilated ICU beds used per year
100%
10%
4.2%
3%
2%
1%
Incremental net monetary benefit (per thousand euros)
10
5
0
0
50
100
150
200
250
300
350
400
450
500
550
600
Daily costs per mechanically ventilated ICU bed Sandman.ICU (€)
Willingness to pay threshold
30,000 €
50,000 €
80,000 €


Intervention effect on mortality (%)
10
7.5
5
2.5
0
Intervention effect on duration of mechanical ventilation (days)
0
1
2
3
Incremental net monetary benefit
40000
30000
20000
10000
0

7.9 Paper Zwerwer et al. (under review)

Mechanical ventilation as a major driver of COVID-19 hospitalization costs: A costing study in a German setting

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4. Health-Ecore, Zeist, The Netherlands
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Email: l.r.zwerwer@rug.nl

Date of submission: November 25, 2023

Keypoints

- While COVID-19 hospitalization costs are essential for policymakers to make informed health care decisions, to date not much is known about these costs in western European countries. In this study we estimated the daily hospitalization costs of COVID-19 patients in Germany for non-ICU and ICU patients.
- Each additional day on the general ward for non-ICU and ICU patients in Germany was found to cost on average € 463.66 and € 414.20, respectively. Additional non-mechanically ventilated days in the ICU, mechanically ventilated days in the ICU and days of ECMO in Germany, were estimated at respectively € 927.45, € 2224.84 and € 350.62.
- This study is the first study estimating COVID-19 hospitalization costs in Germany. Estimated costs were overall in agreement with costs found in literature for non-COVID-19 patients, except for higher estimated costs for mechanical ventilation. These estimated costs can potentially improve the precision of COVID-19 cost effectiveness studies in Germany and will thereby allow health care policymakers to provide better informed health care resource decisions in the future.

Keywords: covid-19, hospitalization costs, Germany, DRG-system, intensive care

JEL classification code: I10

Abstract

Objectives: COVID-19 hospitalization costs were analyzed for a German setting, the main drivers were identified and the development of these costs were tracked over time.

Materials and methods: Administrative costing data was collected for 1,108 COVID-19 patients at Frankfurt University hospital. Costs for each additional day in the general ward and the Intensive Care Unit (ICU) with and without mechanical ventilation (MV) were estimated using generalized linear models with propensity score weighting.

Results: Each additional day in the general ward for non-ICU COVID-19 patients costed €463.66 (SE: 15.89). Costs for each additional day in the general ward and ICU, for ICU patients without and with MV, were estimated at €414.20 (SE: 22.17), €927.45 (SE: 45.52) and €2,224.84 (SE: 70.24).

Conclusion: This is, to our knowledge, the first study examining the costs of COVID-19 hospitalizations in Germany. These estimated costs are essential for policymakers to make informed health care resource decisions.

Compliance with ethical standards

Statements and declarations

The research leading to these results received funding from the European Union's Horizon 2020 programme under grant agreement number: 101015930. The European Union had no involvement in the study design, the data collection, analysis and interpretation of data; in the writing of the report; and in the decision to
submit the article for publication 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) and is advisor to Asc Academics, 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).

Informed consent

The study was conducted in accordance with the Declaration of Helsinki and ethical approval for this study was provided by the Ethical Committee of the University Hospital Frankfurt (Chair: Prof. Dr. Harder, Ref: 2021-36). Written informed consent was routinely obtained from all participants as part of hospital admission.

Data availability

The datasets analyzed during the current study are not publicly available due to privacy of the patients involved, but are available from the corresponding author on reasonable request. The R codes of the models are openly available at RunMyCode.org.

Author contributions

Conceptualization: all authors, data collection: BF, methodology: LRZ, SvdP, ADIvA, BF, formal analysis and investigation: LRZ, SvdP, ADIvA, writing - original draft preparation: LRZ, BF, writing - review and editing: all authors, Funding acquisition: KZ, supervision: SvdP, MjP, KZ, ADIvA, BF.

Acknowledgements

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1. Introduction

In December 2019, the first COVID-19 cases emerged in Wuhan, China [1]. The virus quickly spread around the rest of the world, causing intensive care units (ICU) globally to be overflooded [2–4]. To reduce transmission of the COVID-19 virus, governments across the globe posed several public health and social restrictions [5,6]. During this pandemic, healthcare expenditures rose considerably. For instance, in Germany, healthcare expenditure increased from 2019 to 2020 with 1.1%, compared to an average annual increase of 0.05% in the last decade [7]. Given that over 561,000 German citizens with COVID-19 were hospitalized during the first two years of the pandemic it is reasonable to assume that COVID-19 had a considerable effect on these healthcare expenditures [8,9].

Many hospitalized COVID-19 patients develop severe complications, such as sepsis, acute respiratory distress syndrome and acute kidney injury and are therefore often in need of costly intensive treatments, e.g., mechanical ventilation or kidney replacement therapy [10–12]. Given the substantial number of hospitalized COVID-19 patients as well as the intensive treatment needed for these patients, the costs of hospitalized COVID-19 patients are expected to be considerable [13]. However, little is known about the exact costs of treating for these patients [14–17]. Many researchers use relatively crude estimated average hospitalization costs or costs for related diseases as a proxy for the actual costs of treating COVID-19 patients [13,18–21]. At the same time, the expenditures for treating COVID-19 patients are essential to allow policymakers to make informed health care resource decisions [14,15,22,23].

To date, as far as we are aware, no study examined the costs of hospitalized COVID-19 patients in Germany. Average ICU costs for non-COVID-19 patients have been widely studied, however the costs of an ICU stay varies substantially between studies. For instance, in a multicentre study involving 222 German ICUs, a day on the ICU was valued at € 744 on average (inflated to 2021 using harmonised indices of consumer prices from Eurostat [24], rounded to whole euros) [25]. Tan et al. (2012) found an average of €1,462 per day (inflated to 2021 [24], rounded to whole euros) using a standardized costing methodology in a single German hospital [26]. Comparable costs were found by Martin et al. (2008), who estimated the costs of a day on the ICU in Germany using data from a single ICU to be on average € 1,434 and € 1,786 (both inflated to 2021 [24], rounded to whole euros), respectively without and with mechanical ventilation [27]. In a study involving 51 German ICUs much lower daily costs were found, that is € 901 and € 1,254 (inflated to 2021 [24], rounded to whole euros), respectively without and with mechanical ventilation [28]. Other researchers estimated average daily ICU costs in Germany ranging from € 1,179 - € 1,280 (inflated to 2021 [24], rounded to whole euros) [29,30]. One study assessed the total hospitalization costs for patients with influenza in Germany, which may be most comparable to COVID-19. In a nationwide inpatient sample including non-ICU (93.9%) and ICU (6.1%) patients, the total median costs per patient and per admission were € 1,858 (inflated to 2021 [24], rounded to whole euros) [31].

While literature is available for costs of hospitalized non-COVID-19 patients in Germany, the question remains if these costs can be used as a proxy for the costs of hospitalized COVID-19 patients. Therefore, the aim of the current article is to analyse, from a payer’s perspective [32] with a top-down approach, the costs of hospitalized COVID-19 patients, the main drivers for these costs and the development of these costs over time.

2. Materials and methods

2.1. Data collection

In 2003, the German diagnosis related groups (DRG) system has been introduced, which is a standardized case-based reimbursement system based on diagnoses. For the reimbursement of treatments, all hospitals must provide information based on the International Statistical Classification of Diseases and Related Health Problems edition 10 (ICD-10) and the Operation and Procedure Classification System version 2020. To further develop the DRG system, all hospitals in Germany are obliged under §21 of the Hospital Finance Act (KHG) to forward these data anonymously to the Institute for the Hospital Remuneration System (InEK). For this study, these anonymized data were used. The study was conducted in accordance with the Declaration of Helsinki and ethical approval was provided by the Ethical Committee of the University Hospital Frankfurt (Chair: Prof. Dr. Harder, Ref: 2021-36). All inpatients with a positive SARS-CoV-2 Reverse transcription Polymerase chain reaction (rt-PCR) smear admitted between February 1, 2020 and July 1, 2021 to the University Hospital Frankfurt am Main were included in this study. Most of these patients had COVID-19 as their primary diagnosis. There were no missing data. The total hospitalization costs per patient, overall length of stay (LOS), general ward LOS, ICU LOS, duration of mechanical ventilation and several other treatments, such as duration of extracorporeal membrane oxygenation (ECMO) were recorded for all patients. The total hospitalization costs per patient used in this study were non-negotiable DRG reimbursement fees and would therefore have been similar in all other German hospitals for these same patients. Total hospitalization costs included all hospitalization costs except extrabudgetary compensations (e.g. “Zusatzentgelt”), such as educational infrastructure costs and extrabudgetary compensation for ECMO or dialysis, which can be subjective to negotiation.

a. Pre-processing and descriptive analysis

First, all subjects below the age of 18 years were removed from the data. These patients were excluded from the analysis as clinically speaking they form a different population and receive a materially different treatment for COVID-19 (e.g., paediatric ICU). The sample was split into two parts based on the type of patient: non-ICU or ICU. Non-ICU patients were admitted to the general ward only, ICU patients were admitted to the ICU but could also be in the general ward for part of their hospital stay. Both samples were considered separately for analysis. Descriptive analyses were performed for both samples. Changes in patient characteristics, general ward LOS, ICU LOS, duration of treatments and costs over time were assessed visually.

The Elixhauser comorbidity score was used to examine the comorbidity of patients [33]. The Elixhauser comorbidity score reflects the pre-existing comorbidities in patients. It is a well-established score for risk adjustments. In addition, this score can be used to predict hospital mortality, adverse events, LOS, and hospital discharges [34].

b. Estimating the costs for non-ICU and ICU COVID-19 patients

To estimate the costs for each additional day in the hospital for non-ICU patients and ICU patients we used generalized linear models (GLM). A GLM is a flexible form of an Ordinary Least Square regression as it allows for a link function, which can transform the dependent variable. In addition, different families of error distributions can be used. Consequently, depending on the family of the error distribution, the variance can mathematically depend differently on the mean value. All models used for estimating the costs of an additional day in the hospital were fitted doubly robust [35], meaning that potential confounders were controlled for and a continuous propensity score weighting was applied. Unlike outcome regression or propensity score weighting a doubly robust method assures unbiased estimates when one of the aforementioned models is misspecified. Propensity scores were estimated for the non-ICU patients and the ICU patients separately using covariate balancing propensity score (CBPS) for continuous treatment. In CBPS covariates are balanced by mathematically minimizing the differences in the means and standard deviations between the control and treatment group [36]. The extension of the CBPS for continuous treatment is based on a similar mechanism. However, instead of minimizing means and standard deviations between the treatment and control group the covariance between the treatment and the covariates is minimized [37]. The general ward LOS and duration of mechanical ventilation was taken as the continuous treatment assignment in this study for respectively non-ICU and ICU patients. Hence, all baseline covariates were balanced in such a way that non-ICU patients with a short LOS in the general ward had similar baseline covariates compared to patients with a long general ward LOS. For the ICU sample, baseline covariates were balanced for the duration of mechanical ventilation. Covariate balance was assessed by reviewing the adjusted correlation and analysing adjusted distributional balance in scatterplots and histograms using the R package cobalt [38].

Costs for non-ICU COVID-19 patients were estimated using the subsample of the non-ICU COVID-19 patients. The total hospitalization costs were regressed on the LOS at the general ward and the presence or absence of dialysis using generalized linear models (GLM), while controlling for patient characteristics, the Elixhauser comorbidity score and complications. Complications included myocardial infarction, stroke, intra cerebral bleeding and embolisms, such as pulmonary embolisms and thromboembolisms. The subsample with the ICU patients was used to estimate the costs for the ICU patients. The costs were estimated by regressing the total hospitalization costs on the general ward LOS, the non-mechanically ventilated ICU LOS, and the duration of mechanical ventilation as well as the presence or absence of several other treatments, using GLMs, while controlling for patient characteristics, complications and the Elixhauser comorbidity score. Models were estimated with different error distribution families: Gaussian, Gamma and inverse Gaussian distribution. All models were fitted with the identity link function and the log link function. Both functions were considered plausible candidates for the link function. We hypothesised that costs, excluding the first few days in the hospital, act additively, which would argue for an identity link function. However, considering the non-negativity of the costs data the log link function would be a good second candidate.

Model fit was compared using the Akaike Information Criterion (AIC) and the Bayesian information Criterion (BIC). Moreover, model assumptions were checked using the R package DHARMa [39]. DHARMa uses simulations to create interpretable standardized residuals from a fitted GLM model. These simulated residuals are compared to the residuals of the fitted model. To evaluate the fit and model assumptions of each fitted model we simulated 1,000 residuals and assessed the quantile-quantile (q-q) plots visually. Moreover, a Kolmogorov-Smirnov test was carried out and a dispersion test was performed to check for over or underdispersion. We used the outlier test in DHARMa to check if any of the residuals were significantly different from the simulated residuals. Based on the results on the aforementioned tests, the best fitted GLM family and link function were selected. Moreover, we checked for multicollinearity using the variance inflation factor (VIF). Finally, a sensitivity analysis was performed by deleting all outliers and refitting the model.

All analyses were performed in R version 4.0.3 [40] using libraries dplyr [41], ggplot2 [42], comorbidity [43], regclass [44], CBPS [45], cobalt [38] and DHARMa [39].

3. Results

3.1. Demographics and costs

3.1.1. Admissions

A total of 1,156 inpatients with a positive SARS-CoV-2 rt-PCR smear were included in the study. After removal of all patients below the age of 18 years the data consisted out of 1,108 patients. More specifically, there were 598 non-ICU patients and 510 ICU patients. The majority of the patients was admitted between February 1, 2020 and December 31, 2020, that is, a total of 681 hospital admissions. In 2020, 388 non-ICU patients were admitted to the general ward and 293 patients were admitted to the ICU. In the first half of 2021, 427 patients were admitted to the hospital, of which 210 non-ICU admissions and 217 ICU admissions. A more detailed overview of the hospital admissions can be found in Figure 1, which shows the number of non-ICU and ICU admissions per quarter.

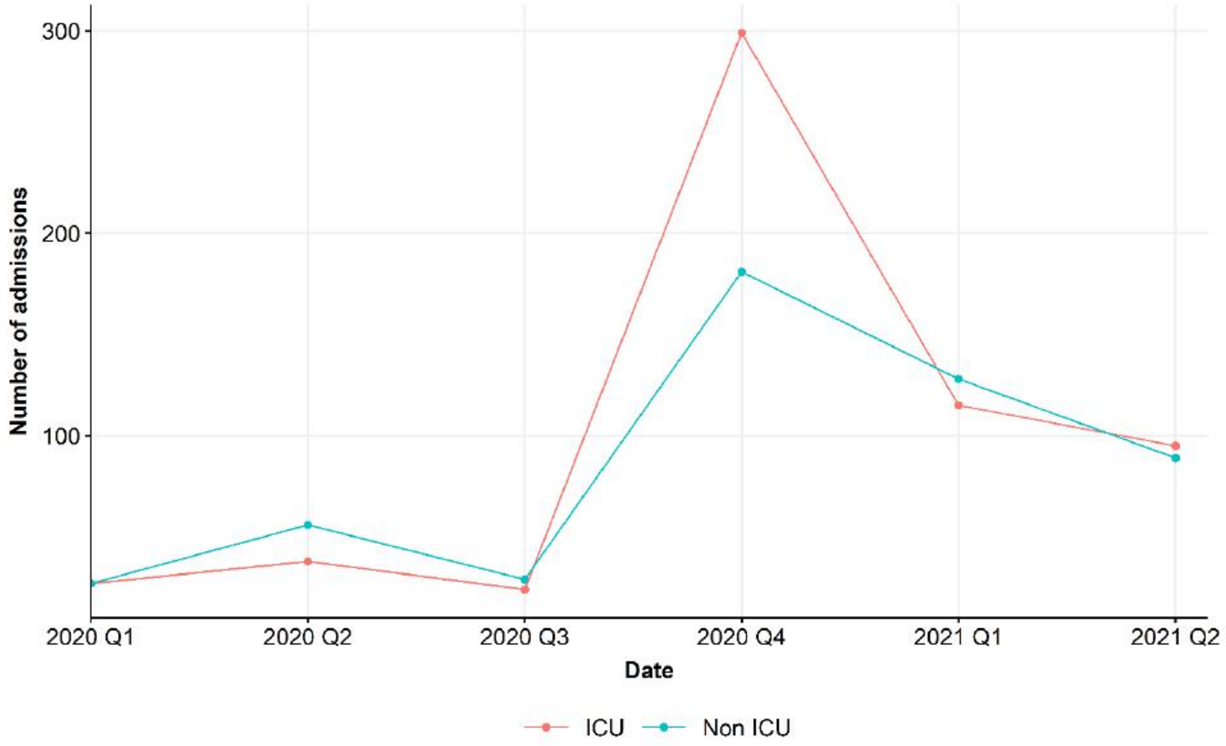

Fig. 1 *Number of non-ICU and ICU admissions over time.*

3.1.2. Basic demographics

Basic demographics of the non-ICU patients, the non-mechanically ventilated and mechanically ventilated ICU patients can be found in Table 1. Overall, patients in the ICU without and with mechanical ventilation were older compared to the non-ICU patients. The majority of patients was male, which was more pronounced in the ICU. Moreover, the Elixhauser comorbidity scores were higher for ICU patients without and with mechanical ventilation compared to non-ICU patients. Overall, most comorbidities like obesity, diabetes, congestive heart failure and chronic pulmonary disease were more common in the ICU. However, cancers were much less frequent in the ICU with mechanical ventilation. This difference was found to be significant.

Table 1. Demographics of the sample.

Characteristics	Total (N=1108)	General ward (N=598)	ICU non-mechanical ventilation (N=124)	ICU mechanical ventilation (N=386)
Age, mean (sd)	60.35 (17.42)	58.24 (18.91)	62.21 (18.92)	63.01 (13.73)
Gender, % male	63.90	55.52	65.32	76.42
Elixhauser comorbidity score, mean (sd)	1.91 (1.87)	1.00 (1.21)	2.40 (1.89)	3.17 (1.91)
Obese (body mass index > 30, %)	*	<1.67^	8.87	11.66
Hypertension (%)	34.57	21.24	49.19	50.52
Diabetic (%)	23.83	16.05	24.19	35.75
Chronic pulmonary disease (%)	7.49	4.52	12.90	10.36
Congestive heart failure (%)	6.32	2.17	10.48	11.40
Cardiac arrhythmias (%)	13.09	7.53	16.94	20.47
Valvular disease (%)	*	<1.67^	<8.06^	2.85
Peripheral vascular disorder (%)	*	<1.67^	<8.06^	6.48
Liver disease (%)	*	2.84	<8.06^	10.88
Aids/HIV (%)	*	2.34	<8.06^	<2.59^
Cancers and lymphoma (%)	6.41	7.86	8.06	3.63
Coagulopathy (%)	*	2.68	<8.06^	32.64
Renal failure (%)	8.39	7.19	12.10	9.07

*Omitted for privacy, ^ten or less patients, censored for privacy.

3.1.3. Demographics over time for non-ICU patients

Figure 2 shows the variation in the average age, average Elixhauser comorbidity score, the proportion of males and the mortality over time for non-ICU and ICU patients. The average age of non-ICU COVID-19 patients showed considerable fluctuation over time. These plots show that non-ICU patients were on average older in the fourth quarter of 2020 and the first quarter of 2021. The Elixhauser comorbidity score and proportion of males for non-ICU patients were relatively stable over time. However, non-ICU patients in the beginning of the COVID-19 pandemic had slightly lower Elixhauser comorbidity scores and were mainly male. The average mortality in the first three quarters of 2020 was zero for non-ICU patients.

3.1.4. Demographics over time for ICU patients

In the ICU, the average age was the highest for patients admitted in the fourth quarter of 2020. ICU patients with on average the highest and lowest Elixhauser comorbidity score were admitted in respectively the second and third quarter of 2020. In the beginning of the pandemic the vast majority of the patients admitted to the ICU was male. Over time this proportion decreased and stabilized around 71%. Finally, mortality was relatively stable over time, fluctuating around an average of 38%.

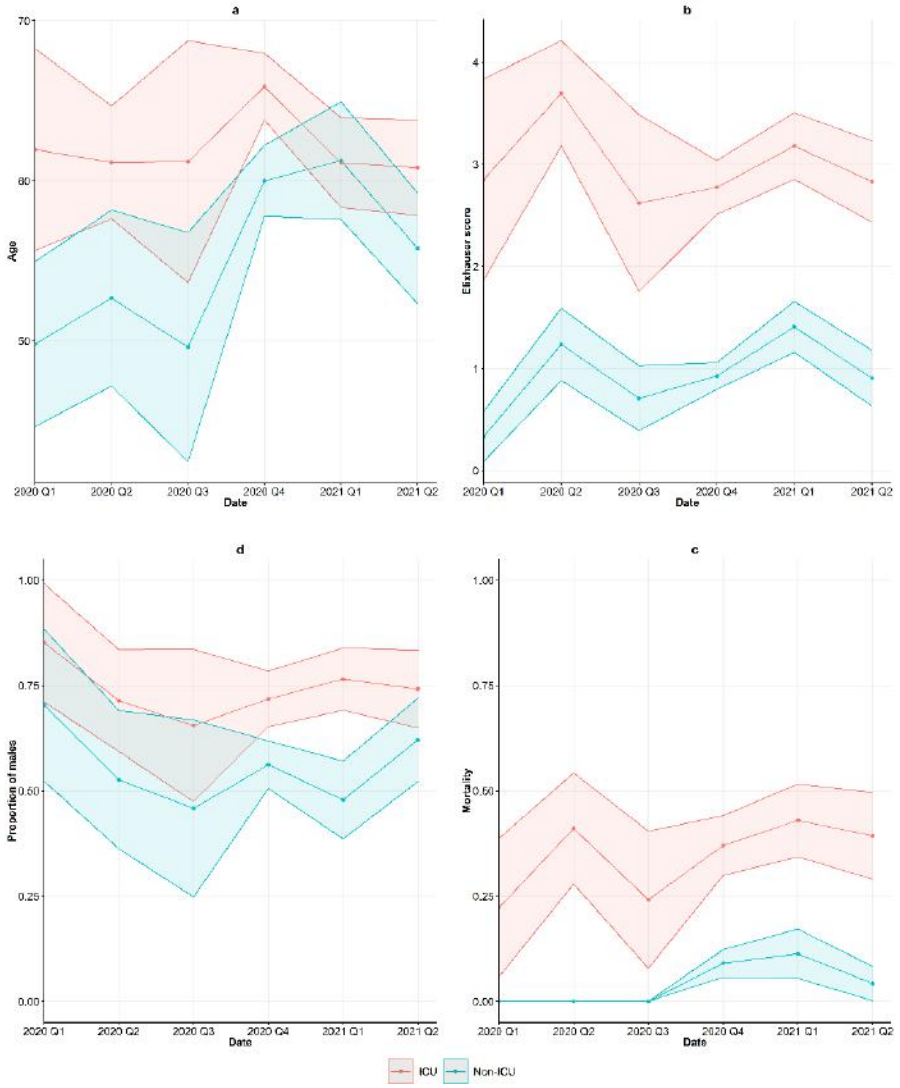

Fig. 2 Observed mean and confidence intervals (CIs) of (a) age, (b) Elixhauser comorbidity score, (c) proportion of males, and (d) average mortalities per quarter for non-ICU patients (blue) and ICU patients (red).

3.1.5. Total hospitalization costs and treatments

Table 2 shows the median costs as well as the median LOS on the general ward and the ICU, the presence or absence of complications, the duration of mechanical ventilation and the duration and or presence/absence of other treatments. Total hospitalization costs per patient for the full sample, that is non-ICU patients and ICU patients, ranged between € 684 and € 209,814 with a median of € 5,103 (interquartile range (IQR): 9,390). More specifically, median total hospitalization costs per non-ICU patients and per ICU patients, without and with mechanical ventilation were respectively € 3,010 (IQR: 3,049), € 5,887 (IQR: 7,825) and € 21,536 (IQR: 35,977).

Table 2. Total costs, LOS, and complications

	Full sample (N= 1,156)	Non-ICU patients (N=598)	Non-mechanically ventilated ICU patients (N=124)	Mechanically ventilated ICU patients (N=386)
Total costs per patient in euros (median, [Q1-Q3])	5,103.05 [2,686.20; 12,076.57]	3,009.75 [2,223.93; 5,272.72]	5,887.36 [3,053.67; 10,879.12]	21,535.83 [7,503.64; 43,480.46]
Total LOS per patient in days (median, [Q1-Q3])	9.00 [5.00;16.00]	7.00 [3.00;10.00]	11.00 [6.00;21.50]	15.00 [9.00;27.00]
General ward LOS in days (median, [Q1-Q3])	5 [1.00;9.12]	7.00 [3.00;10.00]	7.42 [3.08;16.25]	0.50 [0.04;5.54]
ICU LOS in days (median, [Q1-Q3])	0 [0.00;6.96]	NA	2.08 [1.00;3.98]	11.21 [5.62;22.17]
Non mechanical ventilation ICU stay in days (median, [Q1-Q3])	0.00 [0.00;2.46]	NA	2.08 [1.00;3.98]	3.15 [0.46;7.67]
Duration of mechanical ventilation in days (median, [Q1-Q3])	0[0.00;0.50]	NA	NA	5.62 [0.42;15.62]
ECMO duration in days (median, [Q1-Q3])	0[0.00;0.00]	NA	NA	0.00 [0.00;0.00]
Dialysis (%)	*	<1.67^	<8.06^	15.03
Cardiopulmonary resuscitation (%)	*	<1.67^	<8.06^	4.66
Myocardial infarction (%)	*	<1.67^	<8.06^	<2.59^
Stroke (%)	*	<1.67^	<8.06^	<2.59^
Pulmonary embolism (%)	*	<1.67^	<8.06^	<2.59^
Intra cerebral bleeding (%)	*	<1.67^	<8.06^	<2.59^
Embolism/thrombosis (%)	*	<1.67^	<8.06^	<2.59^
Mortality (%)	21.39	7.36	12.10	46.11

*Omitted for privacy, ^ten or less patients, censored for privacy.

3.1.6. Total hospitalization costs and length of stay over time

In Figure 3 we illustrate the median total hospitalization costs per patient, median general ward LOS, median ICU LOS, and median duration of mechanical ventilation over time for both the non-ICU patients as well as the ICU patients. Total hospitalization costs for non-ICU patients were relatively stable over time. In contrast, total hospitalization costs for ICU patients were higher in the first half year of 2020 and the first quarter of 2021. Compared to ICU patients, non-ICU patients had a longer LOS on the general ward. Overall general ward LOS decreased over time for non-ICU patients, while for the ICU patients general ward LOS varied over time with peaks at the first and third quarter of 2020. Remarkably, median general ward LOS for ICU patients in the second quarter of 2020 was less than a day (6.5 hours). ICU LOS and duration of mechanical ventilation over time showed a similar pattern compared to the total hospitalization costs of ICU patients. The ICU LOS and duration of mechanical ventilation peaked in the first two quarters of 2020 and had a slightly lower peak in the first quarter of 2021.

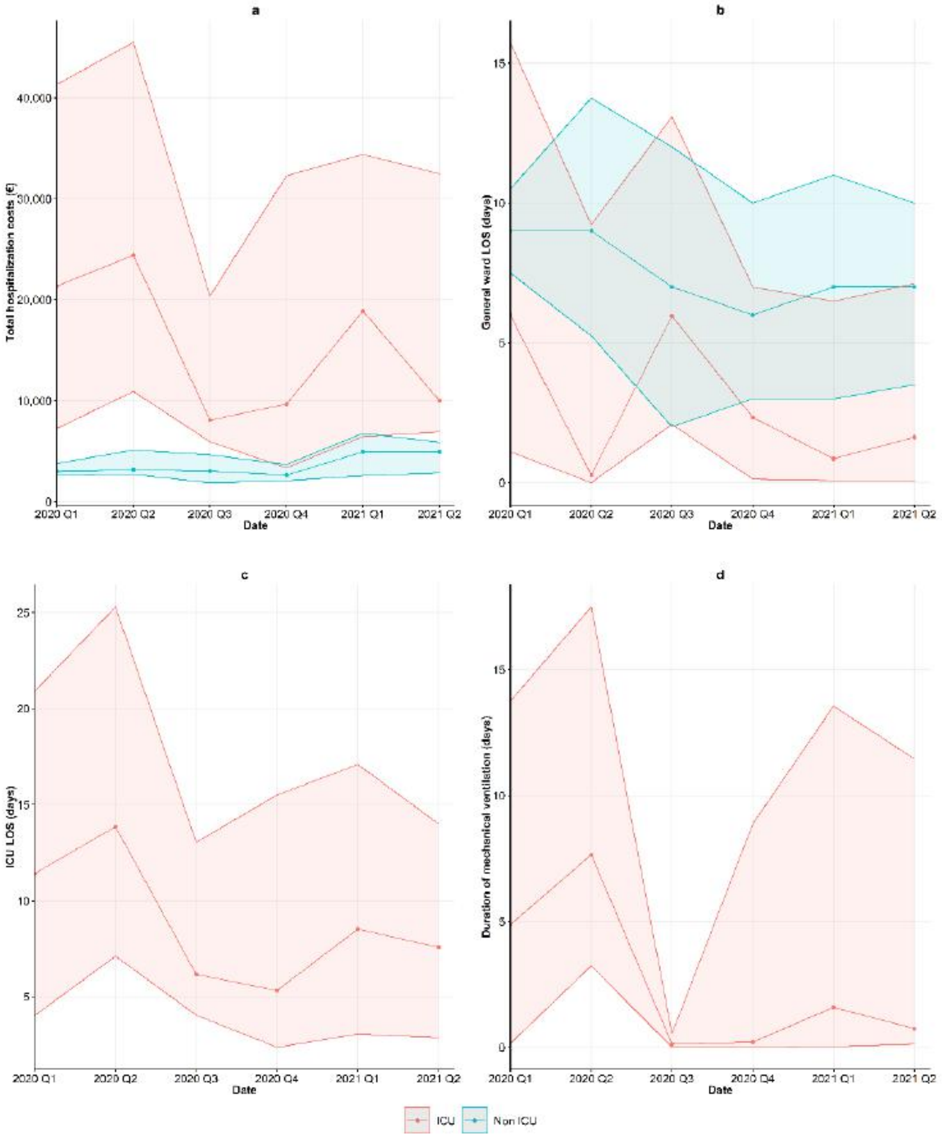

Fig. 3 Observed median (Q1-Q3) of (a) total hospitalization costs, (b) general ward LOS, (c) ICU LOS, and (d) duration of mechanical ventilation over time for non-ICU (blue) and ICU patients (red). Note: ICU LOS and duration of mechanical ventilation were not applicable to non-ICU patients.

a. Estimated costs for non-ICU patients

Costs for an additional day in the general ward were estimated with a GLM for the non-ICU patients. A propensity score model was specified for the LOS in the general ward. We included al pre-treatment covariates that were unbalanced across the LOS in the general ward, that is age, and Elixhauser comorbidity score, in the CBPS. The effective sample size after adjusting for covariate unbalance using the estimated sample weights was 415.69. Covariate balance was assessed by looking at the correlation of the adjusted sample between the LOS in the general ward and each covariate. Moreover, we assessed scatterplots of the LOS in the general ward against both age and the Elixhauser comorbidity. All correlations were reduced to less than 0.1. In addition, the scatterplots showed no relationship between the covariates and the LOS in the general ward in the weighted sample. Hence, all covariates were balanced after applying the propensity score weights created by CBPS.

The AIC and the BIC for the estimated models can be found in the Appendix (Table 5). The AIC and the BIC indicated that a GLM with either a gamma error distribution or an inverse Gaussian error distribution with an identity link or a log link provided the best fit to the data. Model assumptions were checked using the simulated residuals from the DHARMa package. The q-q plots and the results of the Kolmogorov-Smirnov test, dispersion test and outlier test for the gamma and inverse Gaussian error distribution with identity and log link function can be found in the Appendix (respectively Figure 4 and Table 6). The GLM with an inverse Gaussian error distribution provided a better fit to the data compared to the GLM with a gamma error distribution. However, the differences were relatively small. An identity link provided a slightly better fit compared to the log link function according to the q-q plot. The differences between the two link functions were also small. However, while the GLM with an inverse Gaussian error distribution and a log link function showed good dispersion, the residuals of this estimated GLM for patients with increasing LOS blew up (> 10e6), which indicates the unsuitability of the multiplicative nature of the log link function. The GLM with the inverse Gaussian error distribution and identity link function seemed appropriate. The estimated coefficients for this GLM can be found in Table 3. In addition, sensitivity analysis was performed by deleting all outliers. None of the estimated coefficients changed majorly. The estimated GLM without outliers can be found in Table 3. The estimated coefficients were not affected by multicollinearity.

Table 3. Estimated coefficients of GLM with inverse Gaussian error distribution and identity link function for non-ICU patients.

Coefficient (SE)	Full sample	Outliers removed
Constant	726.02 (95.58)***	622.49 (85.34)***
Age	-3.42 (1.50)*	-2.32 (1.33)
Gender female	74.70 (51.60)	87.10 (46.79)
Mortality	329.81 (104.27)**	93.55 (85.23)
Elixhauser comorbidity score	101.98 (22.64)***	79.95 (20.39)***
General ward (days)	463.66 (15.89)***	479.21 (14.76)***
Dialysis	72.49 (487.88)	61.78 (388.05)
Cardiopulmonary resuscitation	-639.31 (122.90)***	-377.82 (104.25)***
Complications	886.21 (852.03)	857.48 (773.09)
Number of samples	598	594
Weighted samples size	415.69	387.88
P value Kolmogorov-Smirnov test	<0.001***	<0.001***
P value dispersion test	<0.001***	<0.001***
P value outlier test	0.03*	1.00

*p<0.05; **p<0.01; ***p<0.001

3.3. Estimated costs for ICU patients

A propensity score model was specified for the duration of mechanical ventilation. We included the age, gender and Elixhauser comorbidity score as covariates in the CBPS. The effective sample size after adjusting for covariate unbalance using the estimated sample weights was 350.57. Covariate balance was assessed by looking at the correlation of the adjusted sample between the duration of mechanical ventilation and each covariate. Moreover, we assessed scatterplots of the duration of mechanical ventilation against both age and the Elixhauser comorbidity and a density plot for each gender. All correlations were reduced to less than 0.1. In addition, the scatterplots and density plots showed no relationship between the covariates and duration of mechanical ventilation in the weighted sample. Hence, all covariates were balanced after applying the weights created by CBPS.

The total hospitalization costs per ICU patient were regressed on the LOS on the general ward, the number of non-mechanically ventilated ICU days, the number of mechanically ventilated ICU days and the presence or absence of several other treatments, such as dialysis, and duration of ECMO, while controlling for patient characteristics, the Elixhauser comorbidity score and complications. The AIC and BIC of the fitted models can be found in the Appendix (Table 7). Evidently a GLM with a gamma error distribution or an inverse Gaussian error distribution with an identity or log link provides the best fit to the data. Model assumptions were checked for these distributions. The q-q plots and the results of the Kolmogorov-Smirnov test, dispersion test and outlier test for the gamma and inverse Gaussian error distribution with identity and log link function can be found in the Appendix (respectively Figure 5 and Table 8). A GLM with a gamma distribution provided the best fit to the data. Moreover, an identity link function provided a better fit compared to the log link function according to the q-q plot and Kolmogorov-Smirnov test. The estimated GLM can be found in Table 4. In addition, sensitivity analysis was performed by deleting all outliers. Except for the Elixhauser comorbidity score, none of the estimated coefficients was majorly affected by the deletion of the outliers. The coefficients of the estimated GLMs can be found in Table 4. None of the estimated coefficients were affected by multicollinearity.

Table 4. Estimated GLM with Gamma error distribution and identity link function for ICU patients.

Coefficient (SE)	Full sample	Outliers removed
Constant	4.61 (289.83)	211.66 (251.34)
Age	-4.24 (4.43)	-2.69 (3.78)
Gender female	-195.12 (206.86)	-299.66 (177.01)
Mortality	363.99 (206.90)	468.38 (186.53)*
Elixhauser comorbidity score	130.60 (56.09)*	-43.39 (53.04)
General ward (days)	414.20 (22.17)***	421.34 (19.21)***
ICU non-mechanical ventilation (days)	927.45 (45.52)***	909.33 (39.41)***
Mechanical ventilation duration (days)	2224.84 (70.24)***	2174.18 (59.54)***
ECMO duration (days)	350.62 (191.73)	440.65 (167.92)**
Dialysis (yes/no)	343.59 (320.11)	287.01 (283.49)
Cardiopulmonary resuscitation	-282.52 (292.87)	-86.80 (251.40)
Complication	2554.40 (1122.82)*	2837.93 (993.46)**
Number of samples	510	506
Weighted sample size	350.57	372.31
P value Kolmogorov-Smirnov test	0.04*	0.83
P value dispersion test	<0.001***	<0.001***
P value outlier test	0.02*	0.08

*p<0.05; **p<0.01; ***p<0.001

4. Discussion

4.1. Main findings

While COVID-19 hospitalization costs are essential for policymakers to make informed health care decisions, to date not much is known about these costs in western European countries. Only two other studies examined the costs of COVID-19 hospitalizations in western Europe. Carrera-Hueso et al. (2021) estimated total hospitalization costs in Spain, respectively per non-ICU patient and per ICU patient at € 60,997 and € 341,845 (adjusted to German 2021 euros, using harmonised indices of consumer prices and purchasing power parities from Eurostat [24,46], rounded to whole euros) [17]. Moreover, in a study including six public health hospitals in Italy daily hospitalization costs were estimated at € 546, € 804 and € 1610 (inflated to German 2021 euros [24,46], rounded to whole euros), for respectively low-complexity care, medium-complexity care and high complexity care [47]. This is, to our knowledge, the first study examining the costs of COVID-19 hospitalizations in Germany. To obtain estimated hospitalization costs of COVID-19 patients in Germany we analyzed administrative data from the University Hospital Frankfurt am Main. Demographics, costs, and treatments were analyzed over time. Each additional day on the general ward for non-ICU and ICU patients was found to cost on average € 463.66 (SE: 15.89) and € 414.20 (SE: 22.17), respectively. Additional non-mechanically ventilated days in the ICU, mechanically ventilated days in the ICU and days of ECMO, were estimated at respectively € 927.45 (SE: 45.52), € 2224.84 (SE: 70.24) and € 350.62 (SE: 191.73).

4.2. Relationship to other hospitalization costs studies

When comparing total COVID-19 hospitalization costs with hospitalization costs of influenza it is evident that the costs for COVID-19 patients are much higher [31]. Moreover, in agreement with the findings of Rapoport et al. (2003), our research showed that ICU LOS is an important driver for hospitalization costs in ICU patients [48]. Other researchers estimated the costs of a day in the ICU for non-COVID-19 patients between €744 and €1,462 (inflated to 2021 [24], rounded to whole euros) [25–30]. The estimated costs for each additional day in the ICU for COVID-19 patients without mechanical ventilation were in accordance with these estimated amounts. In addition, our research showed that the costs for an extra day of mechanical ventilation for COVID-19 patients are more than twice the costs for an additional day in the ICU for non-mechanically ventilated COVID-19 patients. This partly is in agreement with earlier research for non-COVID-19 ICU patients, which showed that mechanical ventilation is a main driver for increased costs of patient care [28,49–51]. However, the estimated daily costs of a COVID-19 patient with mechanical ventilation were higher compared to estimated costs for non-COVID-19 mechanically ventilated ICU patients in Germany [27,28]. In addition, ECMO costs were estimated at € 350.62 (SE: 191.73) per day. These costs were relatively low. Since COVID-19 patients in the ICU are in general severely ill and already have high costs it could be that the use of ECMO did not trigger a higher reimbursement in the case of the COVID-19 related DRG codes. In addition, the extrabudgetary compensation for ECMO was not included in the total hospitalization costs. In Germany, there is a high use of ECMO therapy, possibly caused by this extrabudgetary compensation [52,53]. The amount of this extrabudgetary compensation depends on the patients' characteristics and the severity of the illness and is negotiated individually by each hospital and can vary from € 600 to ten thousands of euros per hospital [54]. Finally, we note that the estimates for the costs of the duration of ECMO had a high standard error, showing quite some uncertainty.

4.3. Strengths and limitations

An extensive study was performed into the costs of COVID-19 patients in Germany. Overall, the cost estimates provide a clear overview of the hospitalization costs for COVID-19 patients in Germany. Cost estimates were based on samples without missing values. Models were fitted doubly robust, that is, controlling for confounding with outcome regression and propensity score weighting. Moreover, sensitivity analysis was performed, and all estimated models were robust against outlier removal. As expected, the estimated coefficient for an additional day in the general ward for the non-ICU patients was relatively close to the estimated coefficient for ICU patients in the general ward. Furthermore, the error distribution of the GLMs for the ICU patients showed reasonable statistical fit. The estimated costs for an extra hospitalization day in this study can be used to estimate the budget impact of COVID-19 hospitalizations in Germany. Possible applications include estimating the saved hospitalization costs by COVID-19 social restrictions or as input parameters for economic models, such as for cost effectiveness studies of COVID-19 vaccinations or novel COVID-19 therapies. Furthermore, utilizing these estimated costs instead of relatively crude estimated average hospitalization costs or costs for related diseases in health economic models will improve the precision of these models and therefore aid health policymakers to make better informed decisions.

Our research was subject to several limitations. Firstly, all the estimated models suffered from underdispersion. However, note that underdispersion is in this case not problematic since it leads to conservative standard errors, i.e., larger confidence intervals [55]. Hence, despite that the estimates are not the most efficient estimates they do give a reasonable impression of the effect on the hospitalization costs. Furthermore, the best fitted GLM for the non-ICU patients had a relatively poor fit. Therefore, the estimated costs for non-ICU patients need to be interpreted with caution. In addition, it would be interesting to compare our estimated costs for non-ICU patients to the costs estimated by the InEK. However, unfortunately these data were not available at the time the current study was performed. Moreover, while we were able to estimate the effect of an additional day in the hospital on the total hospitalization costs, the best fitted model assumes that these costs are constant over time. In reality, the first day of hospitalization is known to be the most expensive. For instance, Rapoport et al. (2003) showed that the first day in the ICU is more than 1.5 times as expensive as later days in the ICU [48]. This effect was not visible in our fitted model. Relatedly, the estimated coefficients for the general ward, ICU and mechanical ventilation duration cannot directly be interpreted as the costs for a day in the hospital as this disregard the effect of age, gender, and comorbidities on the costs. These estimates can rather be interpreted as the effect of one extra day in the general ward or ICU on the total hospitalization costs.

Additionally, we found that for non-ICU patients cardiopulmonary resuscitation (CPR) had a significant negative effect on the costs, while the costs for deceased patients were significantly higher compared to patients who were discharged. However, the vast majority of the patients in the non-ICU sample receiving CPR deceased. Moreover, in the non-ICU sample the number of patients that received CPR was extremely low. Therefore, even though those costs were significantly lower for these patients, the generalizability of the estimated costs for CPR is most likely poor. Furthermore, presence or absence of dialysis did not make a significant difference for the costs of either non-ICU COVID-19 patients nor ICU COVID-19 patients. The total hospitalization costs used in this study excluded the extrabudgetary costs of dialysis, therefore the estimated costs for dialysis are lower than expected. Moreover, the estimated standard errors were relatively large. An explanation for this could be that the dialysis variable included all diverse types of dialysis. The most common types of dialysis in Germany for COVID-19 patients include intermittent haemodialysis and continuous, venovenous, pump-driven haemodialysis [56]. The variation in these dialysis types and the lack of the duration of dialysis in our data could have led to non-significant estimated costs for dialysis. In addition, for the non-ICU COVID-19 patients, the sample contained a small number of patients receiving dialysis. Therefore, the non-ICU COVID-19 sample could have been too limited to provide a narrow confidence interval of the costs for dialysis.

The administrative data in this study was from a single hospital in Germany. In the present study we applied a flat base rate, which is the basis rate for all hospitals in Germany before negotiation. However, the patient population in other hospitals can be different. Ideally, the same modelling approach would be applied to administrative data from other (university) hospitals in Germany. Relatedly, as we are potentially moving towards a post-pandemic situation the patient population might change. However, we controlled for patient characteristics, comorbidities, and complications. Therefore, we expect that these estimated daily costs are generalizable, also after the pandemic. However, the generalizability of the results can be influenced by major changes in the treatment of COVID-19, changes in the population immune response due to vaccinations and infections, and antigenic drift of SARS-CoV-2. Finally, administrative costing data can be subjective to mistakes. Demographics that are not directly relevant for the costs like mild obesity are occasionally underreported [57]. Moreover, administrative costing data do not necessarily reflect the actual costs in a one-to-one way [58]. Reimbursed costs can potentially be lower or higher than the actual costs [59].

5. Conclusion

This study is the first study estimating COVID-19 hospitalization costs in Germany. Estimated costs were overall in agreement with costs found in literature for non-COVID-19 patients, except for higher estimated costs for mechanical ventilation. These estimated costs can potentially improve the precision of COVID-19 cost effectiveness studies in Germany and will thereby allow health care policymakers to provide better informed health care resource decisions in the future.

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Appendix

Table 5. AIC and BIC for estimated GLM's with different error distributions and link functions for non-ICU patients

Family	Link function	AIC	BIC
Gaussian	Identity	10,516.52	10,560.46
Gaussian	Log	10,614.11	10,658.05
Gamma	Identity	36.72	80.66
Gamma	Log	37.09	81.03
Inverse Gaussian	Identity	36.82	80.76
Inverse Gaussian	Log	37.15	81.09

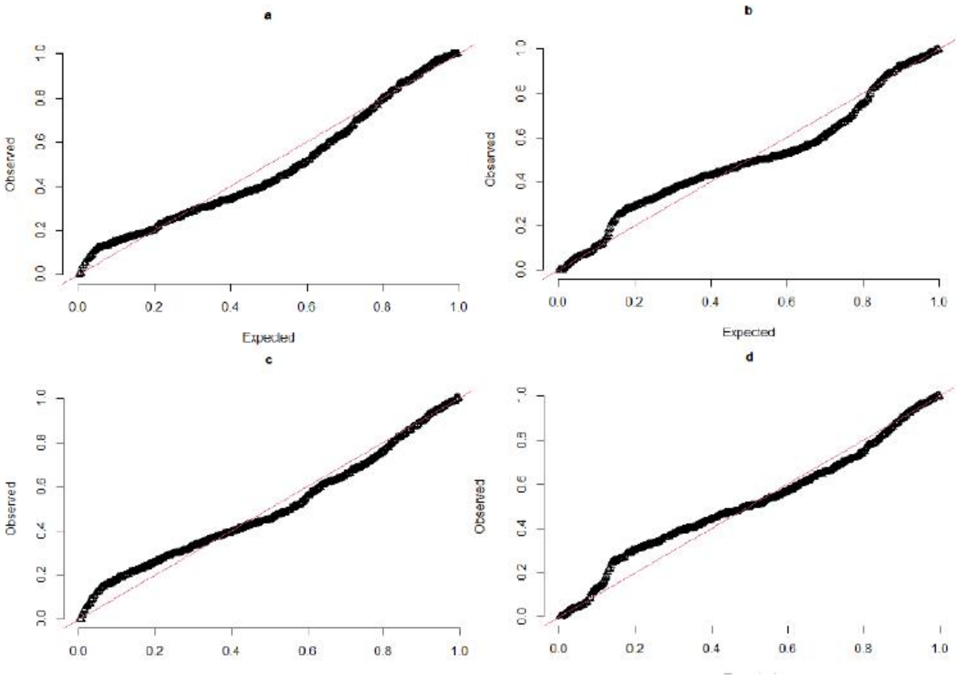

Fig. 4 Q-q plots for non-ICU patients as generated by DHARMa with a. Gamma error distribution with identity link function. b. Gamma error distribution with log link function. c. Inverse gaussian error distribution with identity link function. d. Inverse gaussian error distribution with log link function. The best fit was provided by the GLM with an inverse gaussian distribution with identity link function.

Table 6. Results of Kolmogorov-Smirnov test, dispersion test and outlier test for the gamma and inverse gaussian error distribution with an identity and log link function for the non-ICU patients.

	Gamma (identity)	Gamma (log)	Inverse gaussian (identity)	Inverse gaussian (log)
Kolmogorov-Smirnov test (p-value)	<0.001***	<0.001***	<0.001***	<0.001***
Dispersion test (p-value)	<0.001***	0.14	<0.001***	0.80
Outlier test (p-value)	0.033*	<0.001***	0.033*	0.008**

*p<0.05; **p<0.01; ***p<0.001

Table 7. AIC and BIC for estimated GLM with different error distributions and link functions for ICU patients

Family	Link function	AIC	BIC
Gaussian	Identity	10,535.43	10,590.48
Gaussian	Log	11,479.45	11,534.49
Gamma	Identity	45.80	100.85
Gamma	Log	47.01	102.05
Inverse Gaussian	Identity	46.63	101.68
Inverse Gaussian	Log	47.07	102.12

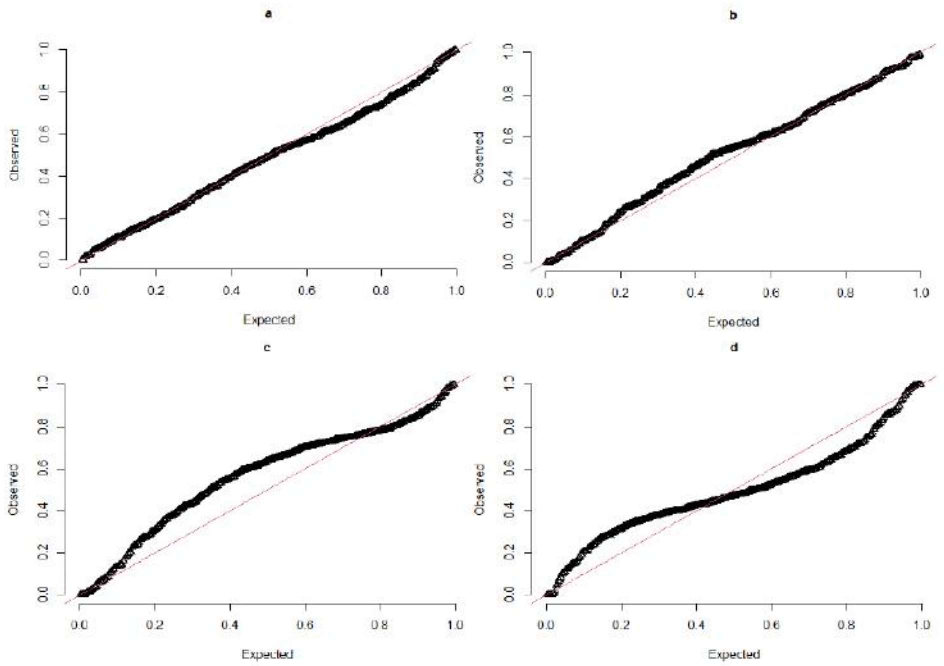

Fig. 5 Q-q plots for ICU patients as generated by DHARMa with a. Gamma error distribution with identity link function. b. Gamma error distribution with log link function. c. Inverse gaussian error distribution with identity link function. d. Inverse gaussian error distribution with log link function. The best fit was provided by a GLM with a gamma error distribution and an identity link function.

Table 8. Results of Kolmogorov-Smirnov test, dispersion test and outlier test for the gamma and inverse gaussian error distribution with an identity and log link function for the ICU patients.

	Gamma (identity)	Gamma (log)	Inverse gaussian (identity)	Inverse gaussian (log)
Kolmogorov-Smirnov test (p-value)	0.040*	0.009**	<0.001***	<0.001***
Dispersion test (p-value)	<0.001***	0.12	<0.001***	0.77
Outlier test (p-value)	0.020*	0.004**	0.003**	<0.001***

*p<0.05; **p<0.01; ***p<0.001