An explorative cost-effectiveness analysis of intensive care and general ward admission for patients infected with COVID-19

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Abstract

Introduction: As a result of the COVID-19 pandemic, there high demand for intensive care (ICU) beds and a shortage of beds arose. The aim of this study is to investigate the cost-effectiveness of an ICU admission for treating COVID-19 versus general ward (GW) admission, together with a hypothetical situation where potential ICU patients did not go to the ICU (no-ICU).

Methodology: The health economic evaluation performed was a cost-effectiveness analysis, in which a model was developed that consisted of a decision tree and a Markov model with a time horizon of one year from hospital admission. The two scenarios investigated were (1) ICU versus GW admission and (2) ICU versus no-ICU admission. In the analysis healthcare costs and health utility values during hospital admission and after discharge were included. Incremental costs and effects were then calculated. The Dutch cost-effectiveness threshold of € 80,000 was used to evaluate if ICU was cost-effective compared to GW and no-ICU based on the incremental cost-effectiveness ratio (ICER). Subgroup analysis based on gender, age (<65 years and ≥65 years), Body Mass Index (<25 and ≥25) and hypertension were performed.

Results: In scenario one, ICU versus GW, the mean total costs were € 43,332 for ICU compared to € 3,947 for GW with total QALY's of 0.393 for ICU compared to 0.501 for GW. It can be indicated that ICU is almost dominated by the GW. For scenario two, ICU versus no-ICU, the total costs of no-ICU were € 5,460 with a total of 0.066 QALY's. The ICER for scenario two was € 115,850. The ICER is higher than the set WTP of € 80,000 therefore it can be indicated that ICU is not cost-effective compared to no-ICU. In the subgroup age <65 in scenario two the ICU may be considered cost-effective.

Discussion & conclusion: It remains unclear which ward adds the most value in terms of costs and health benefits, due to unmeasured factors that could influence the outcome. More research will have to be done on comorbidities related to COVID-19 severity (such as diabetes, lung disease, cardiovascular disease, cancer and smoking) and delayed care due to the COVID-19 pandemic. Reason for this is to gain insight in patients who benefit most from ICU admission in terms of costs and health effects while also better describing a real-world scenario. With these results an ICU manager could make most efficient use of the ICU beds in a subsequent situation such as the COVID pandemic.

Introduction

In December 2019 the first cases of the SARS-Cov-2 virus, also known as COVID-19, were established in China (1). After a rapid spread of the virus around the world, the World Health Organization declared the COVID-19 outbreak on March 11 2020 as a global pandemic (2). As of May 2023, the virus caused more than 750 million cases and almost 7 million deaths worldwide (3). The first case in the Netherlands was registered in February 2020 followed by more than 8 million cases and over 22.000 deaths until May 2023 (4).

During the pandemic, hospitals in the Netherlands were fully occupied. COVID-19 patients were scattered throughout the hospital in general wards (GW), medium care units (MCU) and intensive care units (ICU). A medium care unit, also known as an intermediate care unit, is logistically situated between the ICU and the general ward and can act as a "step up" or "step down" between the general ward and ICU (5). Since many patients infected with COVID-19 needed mechanical ventilation, the demand for ICU care increased and therefore the costs of COVID-19 treatment, because ICU beds cost about three times more than a bed on a general ward (6). The high demand for hospital care of COVID-19 patients caused a shortage of capacity in ICU's and required significant upscaling of intensive care beds, equipment and healthcare personnel. This resulted in high pressure on hospitals and their employees. Due to the high demand for care that COVID-19 caused, the focus has long been on upscaling of care in the short term, with less scrutiny of indications for admission to the ICU (7). To gain insight on the health allocation decisions, a health economic evaluation is particularly useful. Health economic evaluations compare alternative options in terms of their costs and health benefits (8). For this study it would mean the costs and quality of life of patients lying on a general ward and an ICU bed. Until now little can be found in the literature about health economic evaluations aimed at hospital wards with a focus on COVID-19. One study from South Africa appears to also investigate the cost-effectiveness of ICU and general ward and concluded that the ICU was not cost-effective compared to the general ward (9). This study however was performed on a different healthcare system. Furthermore, most published cost-effectiveness studies concern the vaccinations and the vaccination strategy in different countries or policy measures during the COVID-19 waves (10–12).

Future waves of COVID-19 can cause hospitals to make decisions on what care they can provide with the resources that they have at their disposal for their patients. It could therefore be helpful to research the cost-effectiveness because even though a scenario "black", where patients would be selected whether or not to be admitted to the ICU due to an overload of patients, did not occur. With a potential new, more lethal and contagious variant, this could be still a scenario.

Therefore, the aim of this study is to investigate the cost-effectiveness of an ICU admission for treating COVID-19 versus general ward admission. To explore a situation in which there had been no upscaling of ICU beds and thus patients had gone to the general ward, a second scenario is investigated.

Methods

Decision problem and setting

This study was a cost-effectiveness analysis based on a decision model, containing a decision tree and a Markov model (13). The analysis was performed using two scenarios. In the first scenario the cost-effectiveness of the ICU group versus the GW group was compared, by looking at the current policy of hospital admission. In the second scenario the comparison was made between the ICU group and a hypothetical group in which potential ICU patients did not go to the ICU, but to the general ward instead and were therefore named as "no-ICU". The second scenario showed an imitation of the hypothesis of no upscaling of ICU beds. The analysis had a time horizon of one year starting from hospital admission. A time horizon of one year was chosen because there was uncertainty about the long-term health consequences of COVID-19 and one year is sufficient to make a good estimation of the costs and effects. Since the time horizon was no more than one year, no discounting was applied. In this study a healthcare perspective was used considering the costs that are directly related to the hospital departments and all healthcare costs(14). To compare the strategies, primary outcome measures of the analysis consisted of total costs and the total quality-adjusted-life-years (QALY). The QALYs were obtained from multiplying time in a health condition by the utility value of that health condition. The setup of this study was approved by the local review committee of Rijnstate hospital. This study was reported conform the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement (Appendix 1a) (15).

Model structure

A decision tree model linked to a Markov model was developed to evaluate the cost-effectiveness of the treatment strategies general ward admission and ICU admission for COVID-19 patients as shown in Figure 1. The simulated cohort contained 1,000 patients. The decision tree had a length of 152 days (5 months), because the maximum length of stay in the hospital was 123 days. The decision node represents the decision to which treatment ward a patient was admitted; GW or ICU. The branches represent the potential outcomes of the decision node, died or discharged. When a patient was discharged, a distinction was made between being discharged home or discharged to a rehabilitation centre. After rehabilitation a patient went home. When being discharged the presence of long COVID was considered. Based on the decision tree, short-term outcomes were calculated. The outcomes of the decision tree determined where a patient started in the Markov model. Following the decision tree, the model flows into the Markov model to estimate the survival rate, quality of life and costs of discharged people from one year of hospital admission. The Markov model was used to characterize the progression after discharge through health states and their transitions. The three health states of the Markov model were; home and no long COVID, home with long COVID and death. The time horizon of the Markov model is seven months, the remaining time after the five months of the decision tree up to one year after hospital admission. The model had discrete time steps with a cycle length of one month with the assumption that patients move at the end of a cycle.

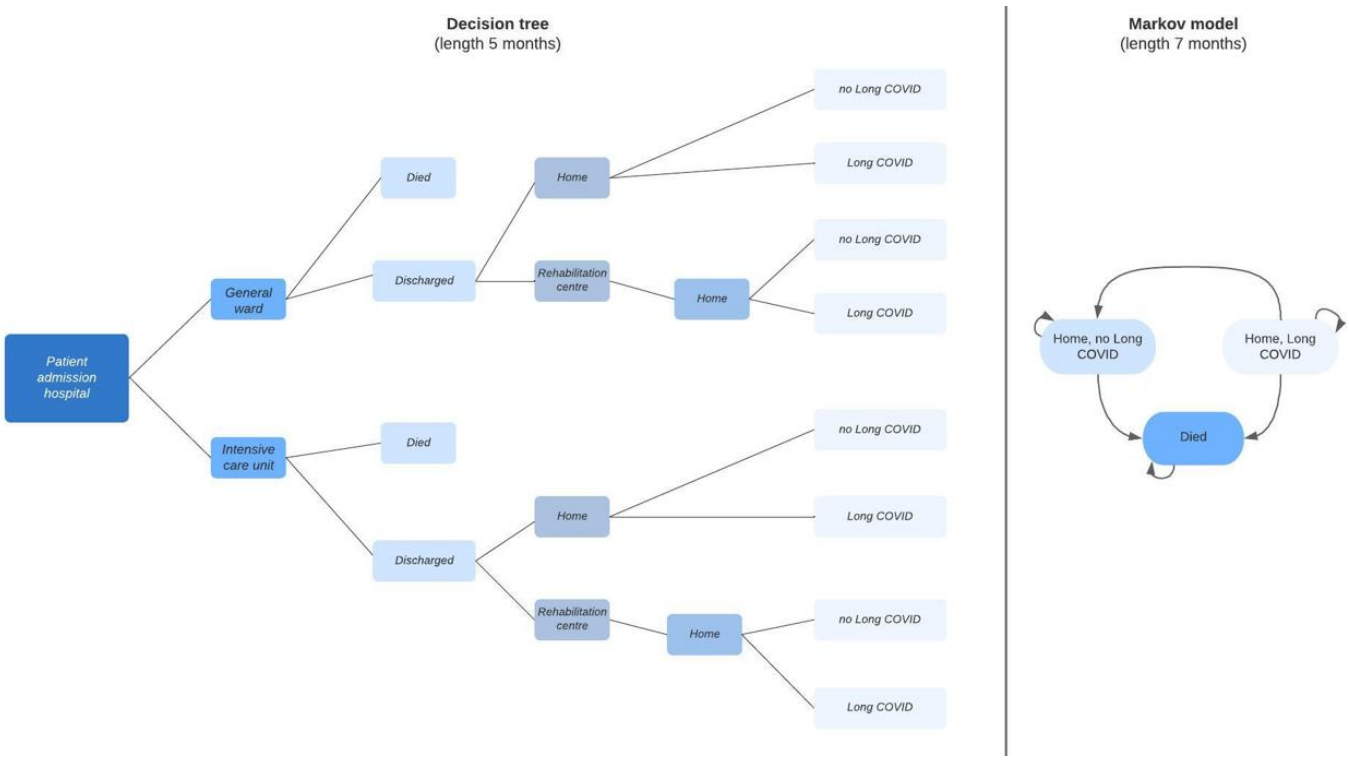

Figure 1: Model structure

<u>Model inputs</u>

The inputs for the model were probabilities, utility values, costs and length of stays. Data about patient characteristics, length of stays in the hospital wards, duration of ventilation and the location a patient was discharged to, were estimated on retrospective data from Rijnstate hospital in Arnhem, The Netherlands. All model inputs are presented in Table 1. Patients who were hospitalized due to an infection with COVID-19 from March 2020 till May 2022 in Rijnstate hospital were included. These patients were selected based on ICD-10 codes related to COVID-19 (U07.1, U07.2 and U09.9) (16). Patients who were in the general ward during admission were assigned to the GW group. All patients who were in the MCU or ICU during admission were assigned to the ICU group, these wards were merged due to the regular exchange of patients between these departments. The analyses were based on 1,296 patients of which 529 (40.8%) were female. Of these 1,296 patients 1,178 patients were in the GW group and 118 in the ICU group. The mean age in the GW was 68 years and 67 years in the ICU.

Probabilities

To calculate the probabilities within the decision tree for the first scenario, a multinomial logistic regression was initially performed. The regression was performed to investigate the relationship between patient characteristics (i.e., age, gender, hypertension and BMI) and the matter of survival and location of discharge (discharged home, discharged to rehabilitation centre and death). The results of the regression can be found in Appendix 3. After reviewing the results with an ICU internist, it was concluded that the face validity of the regression was limited. Therefore, it was decided not to include the regression in further research. As a result, the probabilities within the decision tree were based on the patient data. The probabilities were calculated based on the number of patients in the wards who went home, to rehabilitation and died during admission. Of the patients in the GW 152 (13%) died

during admission, 946 (80%) were discharged home and 80 (7%) were discharged to a rehabilitation centre. In the ICU 34 (29%) died during admission, 59 (50%) were discharged home and 25 (21%) were discharged to a rehabilitation centre.

Since no follow-up information was available, information on long COVID was extracted from literature. In a study of previously hospitalized patients, 76% of patients reported at least one symptom of long COVID after a six-month follow-up (17). Therefore, a probability of 76% was used in the analysis at the end of the decision tree for the presence of long COVID. It was assumed that the presence of long COVID entails additional costs and affects quality of life (18,19).

The transition probabilities used in the Markov model were based on literature. The probabilities of death for all health states were derived from annual mortality numbers of Statistics Netherlands (CBS) (20). A study on long COVID showed a decrease of 15.4% in symptoms within two months for patients who reported at least one symptom of long COVID, this input was used as the transition probability from long COVID to no long COVID for discharged patients (21). All transition probabilities were adjusted to monthly values (22).

Resource-use

In the analysis the estimated various resources used during hospital admission were included based on data of Rijnstate hospital. The length of stay in the hospital ward was included as well as the type of ventilation a patient received, such as Optiflow (high flow nasal oxygen), non-invasive ventilation and mechanical ventilation. Dialysis was also included for patients who were in the ICU. For rehabilitation stay after discharge a mean length of 16.7 days (SE: 1.4) was taken from literature, since no follow-up information was available (23).

Costs

To calculate the hospital costs a detailed cost analysis was performed based on the hospital pathway of the patients (based on data Rijnstate hospital) as seen in Appendix 2 Figure 1. Costs during hospital admission were calculated per patient by multiplying the length of stay in a ward and duration of ventilation and dialysis, with the corresponding price (Table 1). All prices were derived from literature and adjusted for inflation up to 2021 prices using the Dutch consumer price index (24) (CBS). Costs included in the Markov model were the costs per month for being at home and the cost for presence of long COVID.

Utilities

The health state utility values were obtained from the literature and all were elicited from the EQ-5D 3L or 5L (Table 1). A health state utility value was assigned per hospital ward and disutility values were used for the type of ventilation, dialysis and the presence of long COVID. All health state utility values in the decision tree were adjusted to daily values and multiplied by the length of stay and duration of ventilation to calculate QALYs. Health state utility values were also assigned when a patient is at home and when in rehabilitation. In the Markov model the health state utility value for a patient staying at home and the disutility for long COVID were used, these were adjusted to monthly values and multiplied by the time in a health state.

Table 1: Model inputs

	Mean value (%)	Standard error	Distribution	Reference
Patient characteristics				
Number of patients	1296	-		Rijnstate hospital
Gender = female	529 (40.8)	-		Rijnstate hospital
Age (min – max), y	68 (19 – 100)	0		Rijnstate hospital
Hypertension, true	412 (32.8)			Rijnstate hospital
Body mass index	25			Rijnstate hospital
Died, No.	189 (0.14)			Rijnstate hospital
Health state utility values				
General ward hospital bed	0.52	0.104	Beta (α= 0.728, β=0.672)	(25)
MCU/ICU bed	0.40	0.08	Beta (α= 0.8, β= 1.2)	(25)
Rehabilitation	0.611	0.017	Beta (α= 8.074, β=5.140)	(26)
Discharge after hospitalisation	0.648	0.13	Beta (α=0.492, β=0.268)	(27)
Disutility values				
Optiflow/ non-invasive ventilation	0.360	0.072	Beta (α= 0.792, β=1.408)	(28)
Long-covid	0.11	0.022	Beta (α= 0.380, β=3.071)	(18)
Mechanical ventilation	0.560	0.112	Beta (α= 0.672, β=0.528)	(28)
Dialysis	0.269	0.007	Beta (α=7.111, β=19.325)	(29)
Tariff per day (euros)				
General ward bed	524		Fixed	(6)
MCU bed	1362		Fixed	(30)
ICU bed (including diagnostics and medication)	2218		Fixed	(6)
Mechanical invasive ventilation	571		Fixed	(31)
Non-invasive ventilation	341		Fixed	(32)
Optiflow	50		Fixed	(33)
Dialyse	514		Fixed	(34)
Revalidation	506		Fixed	(6)
Long COVID, per month	44.23		Fixed	(19) and (6)
Home, per month	17.52		Fixed	(19) and (6)
Transition probabilities Markov model				
Prob. Home to dead	0.0017		Fixed	(20,22,35)
Prob. Home with long COVID to home no long COVID	0.08	0.016	Beta (α= 0.288 β= 3.312)	(21)
Prob. Home with long COVID to dead	0.0017		Fixed	(20,22,35)
Resource utilization	**Died**	**Died distribution**	**Discharged**	**Discharged distribution**
General ward				
Mean LOS ward, d	7.8	Gamma (α= 1.7, β= 4.5)	5.7	Gamma (α= 1.6, β= 3.5)
Prob. Optiflow Mean LOS optiflow, d	0.0066 0.88	Beta (α= 1 , β= 151) Gamma (α= 4.4, β= 0.2)	0.0010 0.92	Beta (α= 1 , β= 1025) Gamma (α= 4.6, β= 0.2)
Prob. Rehabilitation Mean LOS rehabilitation, d	-	-	0.078 16.7 (1.4)	Beta (α= 80, β= 946) Gamma (α= 192.5, β= 0.1)
ICU				
Prob. Ward Mean LOS ward, d	0.2941 8.12	Beta (α= 10, β= 24) Gamma (α= 1.3, β= 1.3)	1 11.85	Fixed Gamma (α= 2.2, β= 0.7)
Prob. MCU Mean LOS MCU, d	0.5882 4.84	Beta (α= 20, β= 14) Gamma (α= 0.7, β= 6.5)	0.7262 2.09	Beta (α= 61, β= 23) Gamma (α= 0.7, β= 3.1)
Prob. ICU	0.7941	Beta (α= 27, β= 7)	0.8690	Beta (α= 73, β= 11)

Mean LOS ICU, d	13.25	Gamma (α= 0.7, β= 18.3)	15.17	Gamma (α= 2.2, β= 1.1)
Prob. Optiflow Mean duration optiflow, d	0.7059 3.5	Beta (α= 24, β= 10) Gamma (α= 1.3, β= 2.7)	0.6548 4.07	Beta (α= 55, β= 29) Gamma (α= 1.9, β= 2.2)
Prob. NIV Mean duration NIV, d	0.0882 1.4	Beta (α= 3, β= 31) Fixed	0.0357 1.4	Beta (α= 3, β= 81) Fixed
Prob. MIV Mean duration MIV, d	0.4118 16.6	Beta (α= 14, β= 10) Gamma (α= 0.7, β= 23.9)	0.4643 15.99	Beta (α= 39, β= 45) Gamma (α= 1, β= 20.5)
Prob. Dialysis Mean LOS dialysis, d	0.0882 10	Beta (α= 3, β= 31) Gamma (α= 0.6, β= 16.7)	0.0357 13	Beta (α= 3, β= 81) Gamma (α= 5.1, β= 2.6)
Prob. Rehabilitation Mean LOS rehabilitation	-	-	0.2976 16.7	Beta (α= 25, β= 59) Gamma (α= 192.2, β= 0.1)
Mean LOS hospital, d	17.3		27.5	
No-ICU				
Mean LOS ward, d	7.81	Gamma (α=117.3, β=0.1)	27.46	Gamma (α= 258.1, β= 0.1)
Prob. Optiflow Mean LOS optiflow, d	0.7059 0.88	Beta (α= 83, β= 35) Gamma (α= 4.4, β= 0.2)	0.6548 4.07	Beta (α= 77, β= 41) Gamma (α= 38.2, β= 0.1)
Prob. rehabilitation Mean LOS rehabilitation, d	-	-	0.2976 16.7 (1.4)	Beta (α= 35, β= 83) Gamma (α= 192.5, β= 0.1)

Abbreviations

LOS: length of stay **ICU: intensive care unit**
Prob: probability **NIV: non invasive ventilation**
D: days **MIV: mechanical invasive ventilation**

Model assumptions

In both scenarios, it was assumed that patients who had long COVID still incurred additional costs after being discharged from the hospital. First results of a long COVID study of the National Institute for Public Health and the Environment (RIVM) noted that people with long COVID reported higher healthcare utilization in which two out of three people went to their general practitioner and physiotherapist (36). Another study showed a healthcare utilization pre-COVID-19 of 0.4783 and after diagnosis a healthcare utilization of 1.2078 (6,19). These healthcare utilization values were used in this study to calculate the costs for people discharged from the hospital with and without presence of long COVID (6,19).

For the second scenario (ICU versus no-ICU), the assumption was made that 90% of the patients in the no-ICU group would die during admission. This was based on the assumption that these patients would qualify for the ICU and would therefore most likely die without ICU care. The remaining 10% was divided over home and rehabilitation based on the distribution of ICU as it was for the first scenario.

In the second scenario additional assumptions were made to calculate the costs and effects for the no-ICU group. First, the tariff of a general ward bed was used, since it was assumed that the patients were not admitted to the ICU (6). The length of stay in the general ward for the group deceased patients, were derived from the ward as well. It was assumed that patients are sicker than the average ward patient and will therefore die sooner than they would have been in the ICU. The length of stay of the discharged group were derived from the ICU group, because it was assumed that patients spend more time in the hospital before being discharged, compared to a GW patient. For Optiflow, the duration of ventilation and probability were assumed equal to the ICU, because the assumption was that more people on the no-ICU need ventilation.

Analysis

The QALY and costs per patient for each treatment strategy were used to calculate the differences in outcomes between the strategies and then summarized in an Incremental cost-effectiveness ratio (ICER). An ICER is calculated by dividing the difference of costs by the difference in outcomes between the strategies, shown in this equation: $ICER = \frac{\text{Costs strategy A} - \text{Costs strategy B}}{\text{Effects strategy A} - \text{Effects strategy B}}$

The ICER was then compared to the € 80,000 cost-effectiveness threshold, also known as willingness to pay (WTP), of the National Healthcare Institute (37). Due to the high disease burden of COVID-19 in this population, the reference value of the maximum disease burden of € 80,000 per QALY was chosen.

To investigate the impact of parameter uncertainty on the result, a probabilistic sensitivity analysis (PSA) was conducted in which 1,000 simulations were done. For every parameter a distribution was assigned to reflect the uncertainty (Table 1), then a random sample in that distribution was drawn and used as model inputs (38). The simulation was then run and the outputs were analysed. In the analysis different distributions were used. For the probabilities and utilities ranging between zero and one, a Beta distribution was chosen. For the hospital lengths of stays the distribution, Gamma or Lognormal, and parameters were chosen. Based on visual comparison and the goodness-of-fit statistics Akaike Information Criterion, where the lowest value is best, the distribution that fitted the data best was chosen using the R package 'fitdistrplus' (39,40). For distributions when no standard error (SE) was known from literature, a 20% SE of mean was used (13). To fit the statistical distributions when only summary statistics were known, the method of moments was used to calculate parameters of the distribution (41). Prices in the analysis of the decision tree were fixed. Model verification was performed with the TECH-VER checklist and can be found in Appendix 1b (42).

The incremental costs and incremental health outcomes of the PSA were then visualised in an incremental cost effectiveness (ICE) plane. The outcomes of the PSA were used to calculate the Net Monetary Benefit (NMB) for each iteration. The NMB was calculated by multiplying the QALY's with the WTP of € 80,000, minus the costs (41). Using the NMB, a cost-effectiveness acceptability curve (CEAC) was presented with multiple WTPs ranging from € 0 to € 500,000 per QALY. The CEAC indicates the probability that ICU is cost-effective compared to the alternative, general ward or no-ICU. The data analysis was performed with the statistical program Rstudio version 4.2.0 and Excel version 2021 (43). All cost-effectiveness results mentioned in the result section were obtained by the PSAs.

The potential cost-effectiveness of ICU was investigated in eight subgroup analyses. The aim was to investigate in which subgroups ICU admission could be most valuable in terms of costs and effects. The subgroups investigated were gender, age (<65 years and ≥65 years), BMI (<25 and ≥25) and the presence or absence of hypertension. Since BMI data for 609 patients was missing, multiple imputation with five imputations was executed. The pooled result of the five imputations was then used for the subgroup analysis. Model inputs can be found in Appendix 5 Table 1.

Results

Calculation of costs

The results of the detailed cost analysis during hospital admission can be found in Appendix 2. For patients who died during admission in the GW group, the mean total hospital costs per patient were € 4,093 and for patients who were discharged home the mean costs were € 2,836. The difference in costs was due to the longer hospital stay of patients who died. Patients who went to a rehabilitation centre after hospitalisation the total hospital costs were € 4,427. The hospital costs for the ICU group were higher compared to the general ward, with € 32,988 for patients who died during admission and € 24,782 for patients discharged home. The higher costs for patients who died were caused by the longer length of stay on the ICU and the longer duration of mechanical ventilation. The mean total hospital costs for patients who went to rehabilitation after hospitalisation were € 87,299. The no-ICU group had a mean total cost of € 4,123 for patients who died and € 9,846 for patients who were discharged home right after hospitalisation. The mean total hospital costs for patients who went to rehabilitation after hospitalisation were € 25,561. In both the GW and the ICU strategies, the higher hospitalisation costs for patients who went to a rehabilitation centre after hospitalisation, were due to longer hospital stay than the patients who were discharged home. In the ICU this was also caused by longer duration of mechanical ventilation.

Cost-effectiveness analysis

In the first scenario, ICU versus GW, the mean total costs one year after hospital admission were € 43,332 for ICU compared to € 3,947 for GW with total QALY's of 0.393 for ICU compared to 0.501 for GW. The probabilistic ICER was € -363,839. For scenario two, ICU versus no-ICU, the total costs of no-ICU were € 5,460 with a total of 0.066 QALYs and the costs and QALYs for the ICU were equal to the first scenario. The probabilistic ICER for scenario two was € 115,850. This ICER is higher than the WTP set by the National Healthcare Institute of € 80,000, meaning ICU may not be considered cost-effective compared to no-ICU.

The ICE plane of scenario one (Figure 2A) showed that most iterations are in the northwest quadrant, which means overall that ICU is more costly and less effective than the GW. The CEAC (Figure 2B) shows that for no WTP the ICU is cost-effective and therefore the ICU had a probability of zero to be cost-effective compared to GW. In scenario two the ICE plane (Figure 3A) showed that almost all iterations are located in the northeast quadrant, meaning that overall ICU produces more health but also costs more than no-ICU. The CEAC (Figure 3B) shows that with the WTP of € 80,000 the probability of ICU being cost-effective compared to no-ICU is 38%.

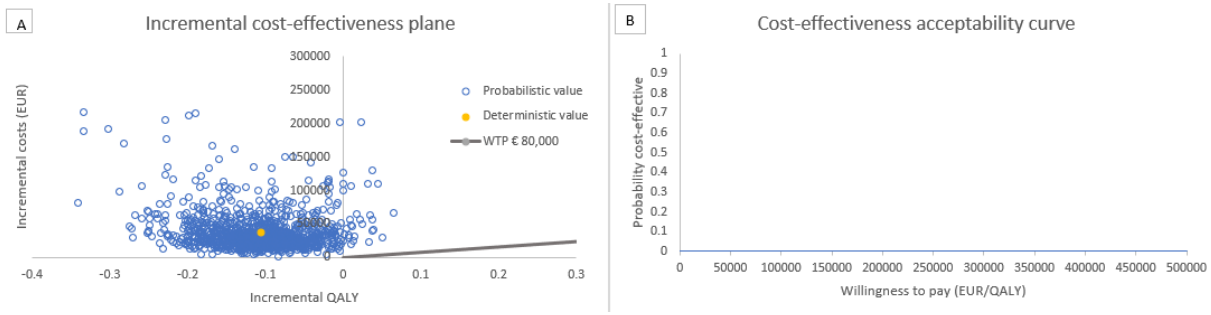

Figure 2: Results scenario one: ICU vs. GW.

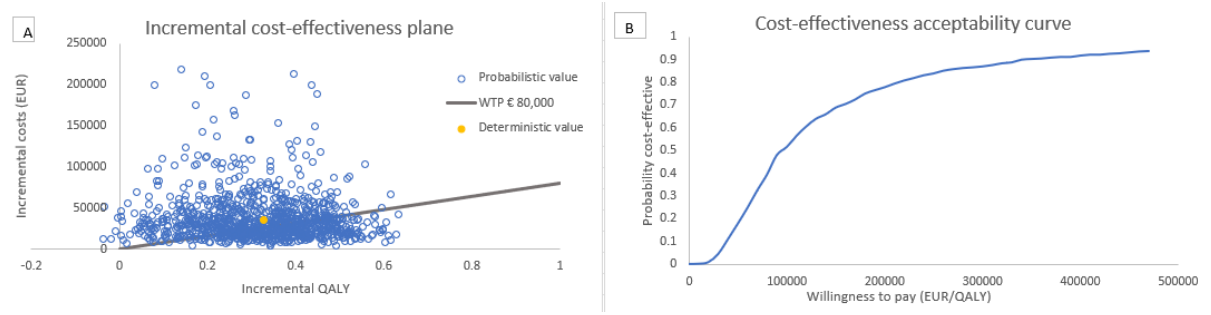

Figure 3: Results scenario two: ICU vs. no-ICU.

Subgroup analysis

Table 2 shows the results of the base case and the subgroup analyses one year after hospital admission. Compared to the base case the following ranges were found on the total costs and total QALY for the GW. The range had a minimum cost of € 2,736 in subgroup age <65 years and maximum costs of € 4,795 for subgroup age ≥65 years. The range of total QALY had a minimum of 0.467 for age ≥65 years and a maximum of 0.553 in subgroup age <65 years. For ICU the minimum costs were € 36,793 in the subgroup age <65 years and the maximum costs were € 50,066 in the subgroup female. The range of total QALY had minimum of 0.345 in the subgroup age ≥65 years and a maximum of 0.474 in subgroup age <65 years. The subgroup analyses showed no difference in cost-effectiveness from the base case analysis for scenario one.

For scenario two the range for the no-ICU group had a minimum cost of € 4,266 for the subgroup age <65 years and a maximum value of € 5,866 for subgroup hypertension. The range of total QALY had a minimum of 0.063 for subgroup female and a maximum of 0.067 for hypertension. In scenario two, the ICER of € 76,512 for the subgroup age <65 years could indicate that ICU is cost-effective compared to no-ICU as the ICER is below the WTP of € 80,000. The ICER for subgroup age <65 can be explained by the large increase in the QALY for ICU (0.474 vs. 0.381) while almost no QALY difference was found in the no-ICU group (0.064 vs. 0.065). The difference in costs had little impact on the ICER, since the costs in the ICU group decreased (€ 36,793 vs. € 42,910) compared to the base case however in the no-ICU group a decrease also can be found in costs (€ 4,277 vs. € 5,470). The decrease in cost in the subgroup age <65 years can be explained by the shorter length of hospital stay. The results of the ICE planes and CEAC of the subgroup analyses can be found in Appendix 5 (figure 5-20).

	Base case	Male	Female	Age <65	Age ≥65	BMI < 25	BMI ≥ 25	Hypertension	No hypertension
N:									
GW	1178	687	491	430	748	533	645	379	799
ICU and no-ICU	118	80	38	41	77	44	74	33	85
Total costs:									
GW	€ 4,078	€ 3,967	€ 4,023	€ 2,736	€ 4,795	€ 4,257	€ 3,770	€ 4,244	€ 3,877
ICU	€ 42,910	€ 39,487	€ 50,066	€ 36,793	€ 45,167	€ 41,727	€ 42,547	€ 43,743	€ 40,688
No-ICU	€ 5,470	€ 5,460	€ 5,330	€ 4,266	€ 5,643	€ 5,399	€ 5,415	€ 5,866	€ 5,193
Total QALY:									
GW	0.491	0.493	0.507	0.553	0.467	0.505	0.480	0.496	0.487
ICU	0.381	0.388	0.397	0.474	0.345	0.406	0.371	0.403	0.375
No-ICU	0.065	0.066	0.063	0.064	0.066	0.065	0.066	0.067	0.065
ICER scenario one	€ -363,839	€ -336,091	€ -422,346	€ -426,942	€ -328,706	€ -379,654	€ -356,942	€ -427,852	€ -328,800
ICER scenario two	€ 115,850	€ 105,839	€ 135,290	€ 76,512	€ 142,025	€ 106,513	€ 121,756	€ 112,756	€ 114,361

Table 2: Probabilistic results base case and subgroup analyses

Discussion

The study performed was a cost-effectiveness analysis consisting of two scenarios. Scenario one (ICU versus GW) showed that the ICU is not cost-effective compared to the GW. The analysis of scenario two (ICU versus no-ICU) resulted in an ICER of € 115,850. Since the ICER is higher than the set WTP of € 80,000 this can indicate that ICU is not cost-effective compared to no-ICU. None of the subgroup analyses showed ICU to be cost-effective, except for the subgroup <65 years old in scenario two. In this case, the ICER was € 76,512 which was caused by the increase in QALY for the ICU group.

The results of the base case analysis could have been foreseen for scenario one, ICU versus GW, as ICU is more expensive than the general ward also survival and quality of life is lower for patients in the ICU. Scenario two investigated a controversial comparison as the assumption of no upscaling in ICU beds was made, therefore patients who otherwise qualified for the ICU went to the general ward. The analysis of the second scenario suggested that it would not be cost-effective to receive ICU care for all patients qualifying for ICU care. In the subgroup analysis, the biggest differences in costs and QALYs compared to the base case analysis were found in the subgroups age for scenario one as previously mentioned in the subgroup analysis section of the results. The relation of costs to both GW and ICU groups for age <65 years old was negative and for age ≥65 years old positive compared to the base case analysis. The opposite was seen in the QALYs of both subgroups of age in GW and ICU. The relation of QALY to GW and ICU for age <65 years old was positive and negative for age ≥65 years old compared to the base case analysis. This could explain why no different cost-effectiveness result was found for these subgroups in scenario one. In scenario two the subgroup analysis of age <65 years old showed an ICER of € 76,512 that could indicate ICU to be cost-effective compared to no-ICU. The reliability of this result can be disputed, since the ICER is just below the threshold of € 80,000 and because strong assumptions were made for scenario two. In order to investigate the reliability of these results in the subgroup analysis age <65 years old, the underlying cause, the increase in QALY for ICU, could be further analysed for age. The stated assumption in the no-ICU of a fixed mortality probability of 0.9 can be refuted for subgroup age <65 years old. In reality the mortality probability could be lower because people younger than 65 years have a higher survival rate than people over 65 years old (44). However, determining the ratio that should be used in the different probabilities of death would be difficult to construct, as no real probability of death for no-ICU is available and would therefore be based on new assumptions.

Comparing study findings and existing literature

Consistent with the results of this study, a previous study mentioned that 63.7% of the patients on the ICU were male, compared to 68% in this study (45). A difference was seen in the ICU mortality percentages, which was 28% in this study and 50% in the previous study. In addition, the ICU LOS in the current study was shorter than the aforementioned study (14.5 SE:1.7 vs. 18 SE:0.6). Another previous study found and that could be compared to this study was a cost-effectiveness study from South Africa (9). The current study resulted in higher hospital costs for ICU compared to no-ICU, this was similar to the found results in the South African study (€ 5,076 for ICU and € 3,701 for the GW group). Their GW group had similarities to the no-ICU group in this study (patients have no access to ICU care due to hypothetical surges of COVID-19). However, instead of a QALY the South African study calculated disability adjusted life years (DALY). A comparison to this study is difficult to make due to the differences in healthcare systems between South Africa and the Netherlands. On the other hand,

the comparisons that can be made are the mortality probability assumption (0.88 compared to 0.9 used in this study) and the identical conclusion that ICU is not cost-effective compared to no-ICU.

Strengths & limitations

A strength of the study was the completeness of data about the patient flow in the hospital. This made it possible to locate where and how long a patient was in a hospital ward and whether that patient used a form of ventilation and duration of ventilation. As a result, almost no assumptions had to be made about patient flows and length of stay. A second strength is the representativeness of the research. The sample of patients used in this study is likely to be representative for the rest of the Netherlands, because the demographic composition of the Arnhem region does not differ much from the rest of the Netherlands (46).

In addition to strengths, there are also some limitations to mention. In the second scenario, the assumption was made for the no-ICU group that 90% of patients would die during hospital admission. Unfortunately, there was no literature on patients who were referred to the ICU but did not go. Therefore, the results of the no-ICU group should be interpreted with caution. A second shortcoming is the limited subgroup analyses that were performed. Initially, the aim of this study was to investigate the effect of known comorbidities related to COVID-19 severity, such as diabetes, hypertension, obesity, lung disease, cardiovascular disease, kidney disease, (history of) cancer and smoking status (47,48), on the outcomes. Unfortunately, the available data only allowed to investigate the subgroups BMI and hypertension of the mentioned known comorbidities to COVID-19 severity. Would it be possible to collect data on the additional comorbidities, better decisions could be made about which patients would benefit most from admission to the ICU. In the event of a possible code black, this would allow informed decisions to be made regarding the use of the hospital's limited resources. Another limitation was the lack of long-term evidence of COVID-19 patients. As a result, a time horizon of one year was chosen. With more evidence about the long-term effects of COVID-19 on patients, fewer assumptions would have been made.

Further research

For further research, it is suggested that data on more comorbidities should be collected and included in the analysis. Possibly an indicator for COVID-19 severity could cause the ICU to be cost-effective but wasn’t included in this study due to lack of data. Including this data, a better analysis can be performed on groups of patients benefitting most from ICU admission. Furthermore, only COVID-19 patients were considered in this study, but in reality, there was also delayed regular care due to the COVID-19 pandemic. A report by the RIVM showed an estimated 320.000 healthy life years lost due to delayed treatments during the COVID-19 pandemic (49). Including these topics in future research the trade-off between assigning an ICU bed to a COVID-19 patient and a qualifying non COVID-19 ICU patient can be investigated. The actual costs for GW and ICU would then be higher due to delayed regular care, since delayed care had negative effects on the health state of patients and thus costs. Furthermore, when determining the QALYs for a GW and ICU patient the loss of QALYs for delayed care of non-COVID-19 patients should be considered. Using these adjustments would better fit the real-world state.

The results of this analysis provides insights on current events based on hospital admission and the hypothetical situation that there was no upscaling of ICU beds. This would allow an ICU manager to make an allocation for the available ICU beds in a subsequent situation such as the COVID-19 pandemic, where a decision needs to be made on which care the hospital can provide. Based on the

subgroup analyses, the found results would mean a preferred allocation for patients age <65 years old for ICU admission, because costs are lower and QALYs are higher for this subgroup.

Conclusion

This study provides insights on the cost-effectiveness of ICU admission for COVID-19 patients. This was investigated using two scenarios: (1) ICU versus GW and (2) ICU versus no-ICU. Admission to the ICU appeared not to be cost-effective compared to GW, since costs for ICU are higher with lower survival and QALYs compared to GW. When comparing ICU to no-ICU, ICU admission also appeared not to be cost-effective with an ICER of € 115,850 which is higher than the WTP of € 80,000. Results from the no-ICU group should be interpreted with caution, because of the strong assumptions made such as the mortality probability of 0.9. It remains unclear which ward adds the most value in terms of costs and health benefits, due to unmeasured factors that could influence the outcome. Therefore, more research will have to be done on comorbidities related to COVID-19 severity and delayed care due to the COVID-19 pandemic. Reason for this is to gain insight in patients who benefit most from ICU admission in terms of costs and health effects while also better describing a real-world scenario.

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Appendix 1: Checklists

1a: CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 2
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Page 3
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Page 4
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 5
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 4
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 4
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 4
Time horizon	9	State the time horizon for the study and why appropriate.	Page 4
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 4
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 4
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 4
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 6
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 6
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 6

Topic	No.	Item	Location where item is reported
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Page 4, 5 & 23
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 9
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Page 9
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	-
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Page 8
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	-
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Page 7 & 8
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 10, 11, 12
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Page 10 & 11
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	-
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Page 13 & 14
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	-
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	-

1b: TECHVER checklist

Test description	Result of the test
Pre-analysis calculations	
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes. Check performed by increasing prices on parameter sheet.
Event-state calculations	
Calculate the sum of the number of patients at each health state	Should add up to the cohort size Yes, cohort size is 1000
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes, checked in PSA results sheet for every iteration
Check if all probabilities are smaller than or equal to one	Yes, checked in PSA results sheet for every iteration
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	With every cycle in model, the number of dead patients is higher than previous period.
Discrete event simulation specific: sample one of the "time to event" types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Sample mean and variance & the simulation outputs should reflect the distribution it is sampled from.
Set all utilities to one Set all utilities to zero	The QALYs accumulated at a given time would be the same as the life years accumulated at that time. Correct No utilities will be accumulated in the model. Correct
Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Lower utilities will be accumulated each time
Set all costs to zero	No costs will be accumulated in the model at any time
Put mortality rates to 0	Patients never die
Put mortality rate extremely high	Patients die in the first few cycles
Set the effectiveness, utility and safety related model inputs for all treatment options equal	Same life years and QALYs should be accumulated for all treatment at any time. Correct
In addition to the inputs above, set cost related model inputs for all treatment options equal	Same costs, life years and QALYs should be accumulated for all treatment at any time. Correct
Change around the effectiveness, utility and safety related model inputs between two treatment options	Accumulated life years and QALYs in the model at any time should be also reversed. Correct
Check if the number of alive patients estimate at any cycle is in line with general population life table statistics	At any given age, the % alive should be lower or equal in comparison to the general population estimate. Correct
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate
Calculate the sum of all ingoing and outgoing transition probabilities	Both should be one
Check if the time conversions for probabilities were conducted correctly.	Yes, performed with literature based calculations.
Decision tree specific: calculate the sum of the expected probabilities of the terminal nodes	Should sum up to one
Patient-level model specific: check if common random numbers are maintained for sampling for the treatment arms?	Yes
Patient-level model specific: check if correlation in patient characteristics is taken into account when determining starting population?	Yes
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period

	when the treatment is administered
Population model specific: set the mortality and incidence rates to zero	Prevalence is constant in time
Result calculations	
Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less effective treatments. Correct, negative incremental qaly's in scenario 1, because GW is more effective. In scenario 2 positive incremental QALY's, icu is more effective.
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs. Correct for both scenarios.
Total life years > total quality adjusted life years	Yes
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes, checked by removing cycles from analysis.
Is the reporting and contextualization of the incremental results correct?	The use of the terms such as: "dominant"/ "dominated"/ "extendedly dominated"/ "cost-effective" etc. should be in line with the results. In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment. Correct
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes
If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes
Set mortality rate to zero	No patients die
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	The results would be the same as the results when AE rate is set to zero.
Divide total undiscounted treatment acquisition costs by the average duration on treatment.	Not applicable
Set discount rates to a higher value	Not applicable
Set discount rates of costs/effects to an extremely high value	Not applicable
Put adverse event/discontinuation rates to zero and then to extremely high level.	Not applicable
Double the difference in efficacy and safety between new intervention and comparator and report the incremental results.	Approximately twice of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism
Do the same for a scenario in which the difference in efficacy and safety is halved.	Approximately halve of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism
Uncertainty analysis calculations	
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower bound) - standard error and not standard deviation used in sampling - Lognormal / gamma distribution for hazard ratios and costs/ resource use	Yes

- Beta for utilities and proportions/probabilities - Dirichlet for multinomial - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) - Normal for other variables as long as samples don't violate requirement to remain positive when appropriate	
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No. A small discrepancy is in ICU, but can be explained by the many parameters and their uncertainty.
If you take new PSA runs from the excel model do you get similar results?	Yes. When running new PSA the deterministic and probabilistic results are similar.
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes.
Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape?	There are some data points outside the cloud, but this can be explained by the fact that a number of parameters have a large range.
Is the sum of all CEAC lines equal to 1 for all WTP values?	Not applicable, only using one WTP for CEAC.
Are the explored scenario analyses provide a balanced view on the structural uncertainty? (i.e. not always looking at more optimistic scenarios)	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter, use graphical methods to examine distributions, functions	The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution functions (e.g. Normal, Gamma, etc.)
Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon).	No
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected)	Yes
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Are comparable
OWSA=one-way sensitivity analysis; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; WTP = willingness to pay; CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; LY = life years; QALYs = Quality adjusted life years; OR = odds ratio; RR= relative risk; HR = hazard ratio	

Appendix 2: Additional figures and tables

Figure 1: Hospital pathway cost utilization scenario 1

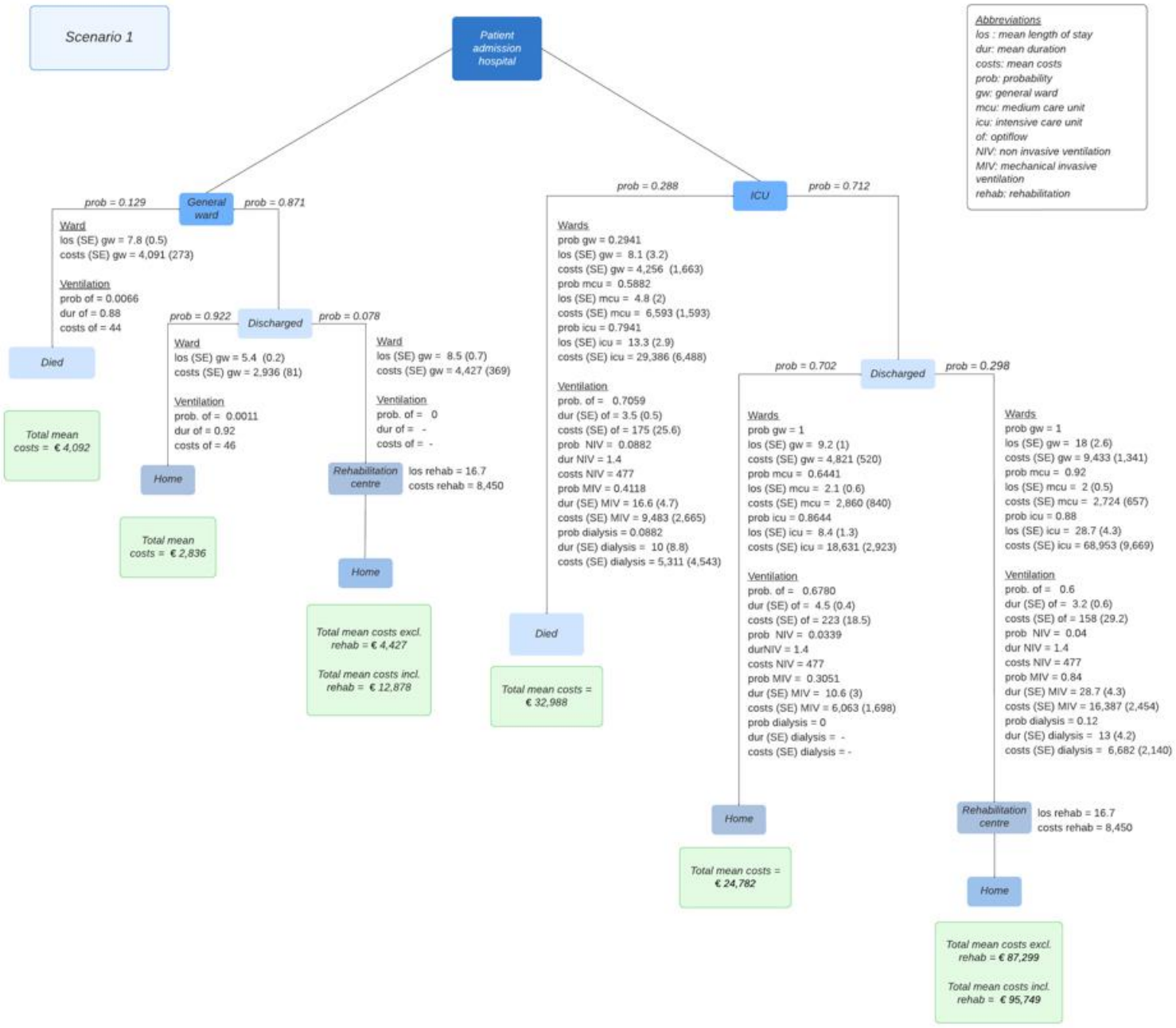
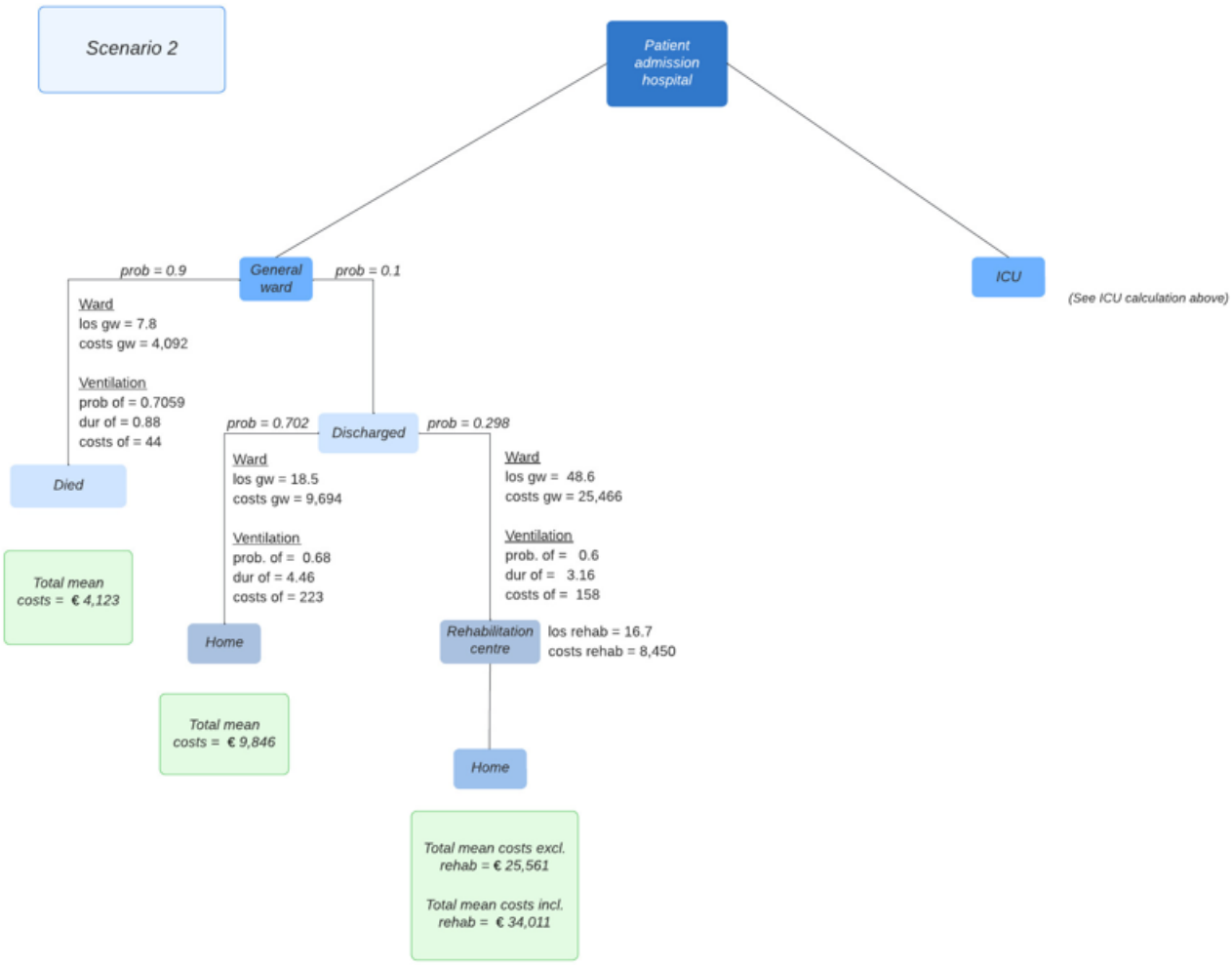


Figure 2: Hospital pathway cost utilization scenario 2



Appendix 3: Multinomial logistic regression

To calculate the probabilities within the decision tree for the first scenario (ICU versus GW), a multinomial logistic regression was originally performed. The aim was to correct for patient characteristics so that the probability of the different events is corrected for differences between the groups. With these outcomes, the aim was to make less biased comparisons between the groups, in addition to perform a subgroup analysis based on patient characteristics.

The dependent variable was survival and destination of discharge when survived (discharged home, discharged to a rehabilitation centre or died). The independent variables were chosen based on literature, expert opinion and data available (i.e., gender, age, BMI and hypertension).

To check for separation of the data, plots were made of the patient characteristics on the end states (discharged home, discharged to a rehabilitation centre or died). The plots can be found in figure 3 below. Separation would occur if one or more of the patient characteristics would predict the outcomes perfectly. It can be seen in the plots that for each end state all properties of the patient characteristic are represented. Therefore, it can be concluded that there is no separation in any of the patient characteristics.

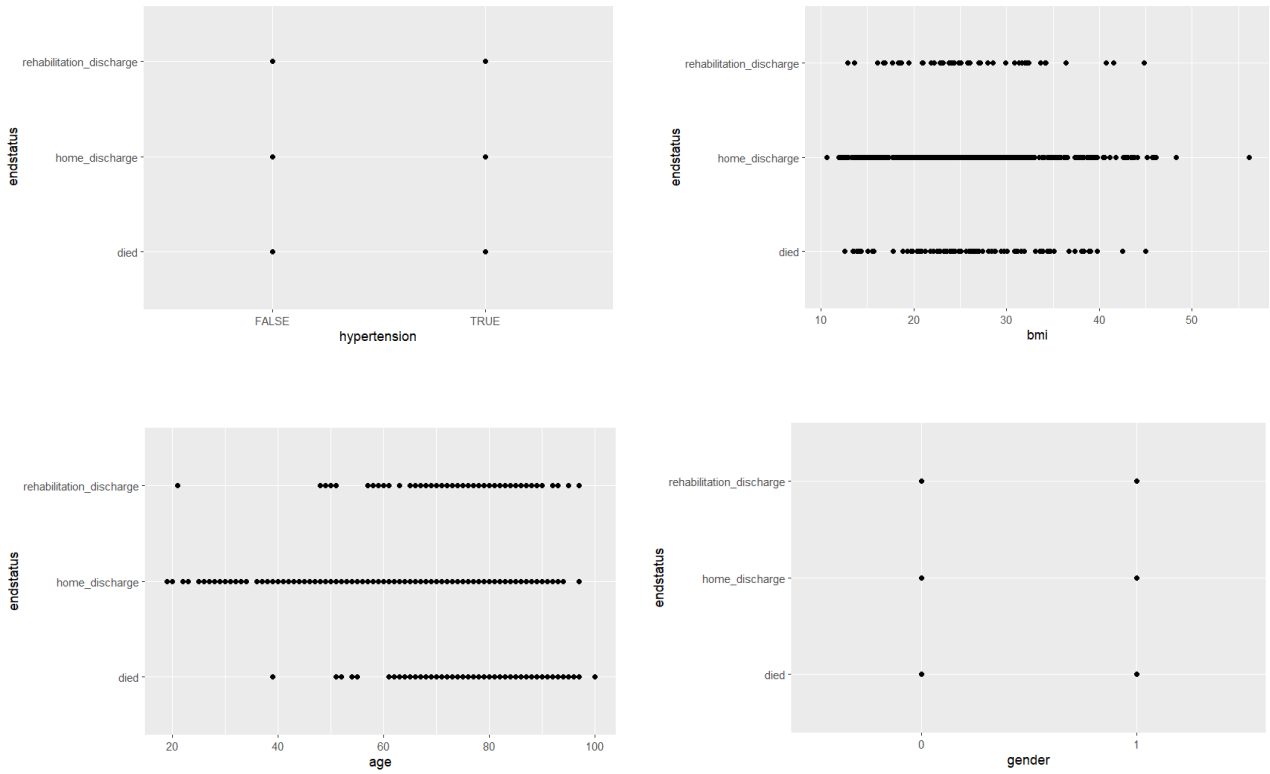


Figure 4. Plots of patient characteristics

For BMI 609 of the 1,296 patients had missing values, therefore multiple imputation was used to handle these missing values in the regression. Multiple imputation was performed using the R package "mice" and 5 imputation sets (50). With the results of the 5 imputations of the regression, predictions were made based on the average ICU patient to equalize the groups. The average ICU patient was 67 years old, male, with a BMI of 27 and no presence of hypertension. The average of these predictions was calculated as the probabilities of the decision tree. Table 3 below shows the values of the pooled predictions and the values calculated with the patient data for comparison.

Patient data observed		
End status	*Prob. General ward*	*Prob. ICU*
Died	0.129	0.288
Home	0.8031	0.5
Rehabilitation	0.0679	0.212
Predictions based on regression		
End status	*Prob. General ward*	*Prob. ICU*
Died	0.086 (Sd: 0.0065)	0.3195 (Sd: 0.0047)
Home	0.8737 (Sd: 0.0004)	0.5010 (Sd: 0.0140)
Rehabilitation	0.0396 (Sd: 0.0069)	0.1699 (Sd: 0.0153)

Table 2. Probabilities decision tree

It can be seen in the table that despite correcting for patient characteristics in the regression, there is little difference between the probabilities. After consulting with an internist from Rijnstate hospital it was decided not to use this regression. It was expected that by correcting for these variables more patients would die in the GW group. It can be concluded, based on low face validity, that the correct predictors were not included in the study that would influence the outcome.

Appendix 4: Cost-effectiveness analysis

Deterministic results

Based on the deterministic results the total costs after one year are € 41,573 for ICU compared to € 4,041 for general ward. The total QALYs for ICU are 0.393 and 0.500 for the general ward. With incremental costs of € 37,532 and incremental effects of -0.11.

In the second scenario, the mean costs after one year of no-ICU admission are € 5,450 with total QALYs of 0.066. The incremental costs are € 36,123 and incremental effects are 0.33, this resulted in an ICER of € 110,382 ICU compared to no-ICU.

Appendix 5: Subgroup analysis

Table 1: Model inputs

Gender	**Male**		**Female**	
General ward	*Died = 0.142*	*Discharged = 0.871*	*Died = 0.112*	*Discharged = 0.880*
Prob. Ward	1	1	1	1
Mean LOS ward, d	8.32	5.78	6.91	5.47
Prob. Optiflow	0.010	0.002	-	-
Mean duration optiflow, d	0.88	0.92	-	-
Prob. Rehabilitation	-	0.058	-	0.094
Mean LOS rehabilitation		16.7	-	16.7
ICU	*Died = 0.300*	*Discharged = 0.700*	*Died = 0.263*	*Discharged = 0.737*
Prob. Ward	0.250	1	0.4	1
Mean LOS ward, d	12.92	10.58	0.93	14.39
Prob. MCU	0.583	0.679	0.6	0.821
Mean LOS MCU, d	4.55	1.74	5.55	2.69
Prob. ICU	0.833	0.893	0.7	0.821
Mean LOS ICU, d	12.95	13.37	14.11	19.37
Prob. Optiflow	0.750	0.679	0.6	0.607
Mean duration optiflow, d	3.61	4.26	3.15	3.78
Prob. NIV	0.125	0.054	-	-
Mean duration NIV, d	1.4	1.4	-	-
Prob. MIV	0.375	0.393	0.5	0.607
Mean duration MIV, d	19.1	20.3	12.16	20.47
Prob. Dialysis	0.125	-	-	0.107
Mean LOS dialysis, d	10.3	-	-	13
Prob. Rehabilitation	-	0.268	-	0.357
Mean LOS rehabilitation	-	16.7	-	16.7
No-ICU	*Died = 0.9*	*Discharged = 0.1*	*Died = 0.9*	*Discharged = 0.1*
Prob. Ward	1	1	1	1
Mean LOS ward, d	8.32	23.7	6.91	32.51
Prob. Optiflow	0.750	0.679	0.6	0.607
Mean duration optiflow, d	0.361	4.26	3.15	3.78
Prob. Rehabilitation	-	0.268	-	0.357
Mean LOS rehabilitation	-	16.7	-	16.7
Age	**< 65 years**		**≥ 65 years**	
General ward	*Died = 0.016*	*Discharged = 0.984*	*Died = 0.194*	*Discharged = 0.806*
Prob. Ward	1	1	1	1
Mean LOS ward, d	6.05	4.07	7.89	6.76
Prob. Optiflow	-	-	0.007	0.001
Mean duration optiflow, d	-	-	0.88	0.92
Prob. Rehabilitation	-	0.016	-	0.121
Mean LOS rehabilitation	-	16.7	-	16.7
ICU	*Died = 0.122*	*Discharged = 0.878*	*Died = 0.367*	*Discharged = 0.623*
Prob. Ward	0.4	1	0.276	1
Mean LOS ward, d	0.95	9.92	9.90	13.29
Prob. MCU	0.6	0.611	0.586	0.813
Mean LOS MCU, d	4.4	1.73	4.92	2.30
Prob. ICU	0.8	0.917	0.793	0.833
Mean LOS ICU, d	11.4	12.48	13.50	17.60
Prob. Optiflow	0.6	0.694	0.724	0.625
Mean duration optiflow, d	4.14	4.31	3.40	3.94
Prob. NIV	-	0.028	0.103	0.042
Mean duration NIV, d	-	1.4	1.4	1.4
Prob. MIV	0.6	0.333	0.379	0.563
Mean duration MIV, d	12.8	21	17.70	20.00
Prob. Dialysis	0.4	0.028	0.035	0.042
Mean LOS dialysis, d	14.5	11	2.00	14.00
Prob. Rehabilitation	-	0.222	-	0.354

Mean LOS rehabilitation	-	16.7	-	16.7
No-ICU	*Died = 0.9*	*Discharged = 0.1*	*Died = 0.9*	*Discharged = 0.1*
Prob. Ward	1	1	1	1
Mean LOS ward, d	6.05	22.42	7.89	29.83
Prob. Optiflow	0.6	0.6944	0.724	0.625
Mean duration optiflow, d	4.14	4.14	3.40	3.94
Prob. Rehabilitation	-	0.222	-	0.354
Mean LOS rehabilitation	-	16.7	-	16.7
BMI	**BMI <25**		**BMI ≥ 25**	
General ward	*Died = 0.105*	*Discharged = 0.895*	*Died = 0.149*	*Discharged = 0.851*
Prob. Ward	1	1	1	1
Mean LOS ward, d	7.99	5.8	7.7	5.51
Prob. Optiflow	0.018	-	-	0.002
Mean duration optiflow, d	0.88	-	-	0.92
Prob. Rehabilitation	-	0.096	-	0.062
Mean LOS rehabilitation	-	16.7	-	16.7
ICU	*Died = 0.250*	*Discharged = 0.750*	*Died = 0.311*	*Discharged = 0.689*
Prob. Ward	0.182	1	0.348	1
Mean LOS ward, d	8.34	12.03	8.07	11.73
Prob. MCU	0.636	0.697	0.565	0.745
Mean LOS MCU, d	4.22	2.19	5.18	2.04
Prob. ICU	0.727	0.939	0.826	0.824
Mean LOS ICU, d	18.69	13.14	10.96	16.83
Prob. Optiflow	1	0.758	0.565	0.588
Mean duration optiflow, d	3.44	4.08	3.54	4.13
Prob. NIV	0.091	0.067	0.087	-
Mean duration NIV, d	1.4	1.4	1.4	-
Prob. MIV	0.364	0.485	0.435	0.451
Mean duration MIV, d	15.45	18.02	17.10	22
Prob. Dialysis	-	-	0.130	0.039
Mean LOS dialysis, d	-	-	10.33	9
Prob. Rehabilitation	-	0.212	-	0.353
Mean LOS rehabilitation	-	16.7	-	16.7
No-ICU	*Died = 0.9*	*Discharged = 0.1*	*Died = 0.9*	*Discharged = 0.1*
Prob. Ward	1	1	1	1
Mean LOS ward, d	7.99	25.90	7.70	27.11
Prob. Optiflow	1	0.7576	0.565	0.588
Mean duration optiflow, d	3.44	4.08	3.54	0.353
Prob. Rehabilitation	-	0.212	-	0.353
Mean LOS rehabilitation	-	16.7	-	16.7
Hypertension	**Absence of hypertension**		**Presence of hypertension**	
General ward	*Died = 0.134*	*Discharged = 0.866*	*Died = 0.119*	*Discharged = 0.881*
Prob. Ward	1	1	1	1
Mean LOS ward, d	7.51	5.49	8.53	5.97
Prob. Optiflow	0.009	0.001	-	-
Mean duration optiflow, d	0.88	0.92	-	-
Prob. Rehabilitation	-	0.074	-	0.077
Mean LOS rehabilitation	-	16.7	-	16.7
ICU	*Died = 0.306*	*Discharged = 0.694*	*Died = 0.242*	*Discharged = 0.712*
Prob. Ward	0.346	1	0.125	1
Mean LOS ward, d	7.89	11.31	10.26	13.11
Prob. MCU	0.577	0.712	0.625	0.760
Mean LOS MCU, d	5.64	2.33	2.45	1.58
Prob. ICU	0.846	0.881	0.625	0.840
Mean LOS ICU, d	13.27	14.41	13.17	17.4
Prob. Optiflow	0.692	0.644	0.750	0.680
Mean duration optiflow, d	3.97	4.1	2.06	4.13
Prob. NIV	0.077	0.017	0.125	0.080
Mean duration NIV, d	1.4	1.4	1.4	1.4

Prob. MIV	0.385	0.441	0.500	0.520
Mean duration MIV, d	16.55	20.02	16.80	21
Prob. Dialysis	0.077	0.051	0.125	-
Mean LOS dialysis, d	15	13	1	-
Prob. Rehabilitation	-	0.288	-	0.320
Mean LOS rehabilitation	-	16.7	-	16.7
<u>No-ICU</u>	*Died = 0.9*	*Discharged = 0.1*	*Died = 0.9*	*Discharged = 0.1*
Prob. Ward	1	1	1	1
Mean LOS ward, d	7.51	25.67	8.53	28.93
Prob. Optiflow	0.692	0.644	0.750	0.680
Mean duration optiflow, d	3.97	4.10	2.06	4.13
Prob. Rehabilitation	-	0.288	-	0.320
Mean LOS rehabilitation	-	16.7	-	16.7

Appendix 5A: results subgroup analysis

<u>Results subgroup male</u>

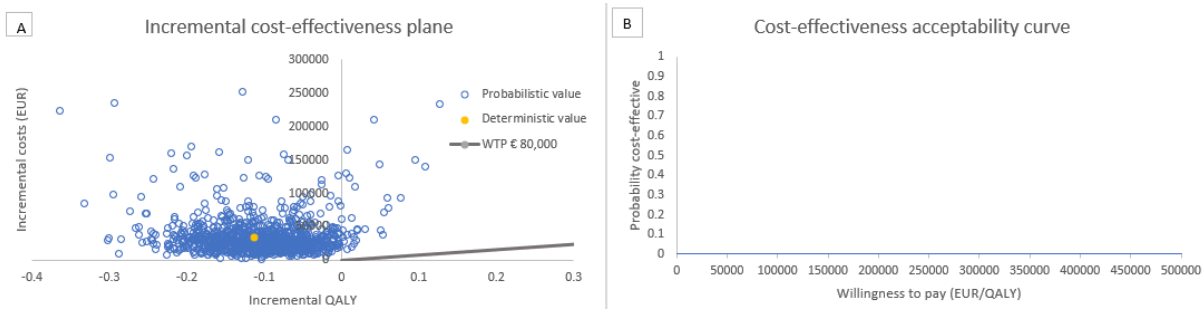


Figure 5: Subgroup male. ICE plane and CEAC scenario 1

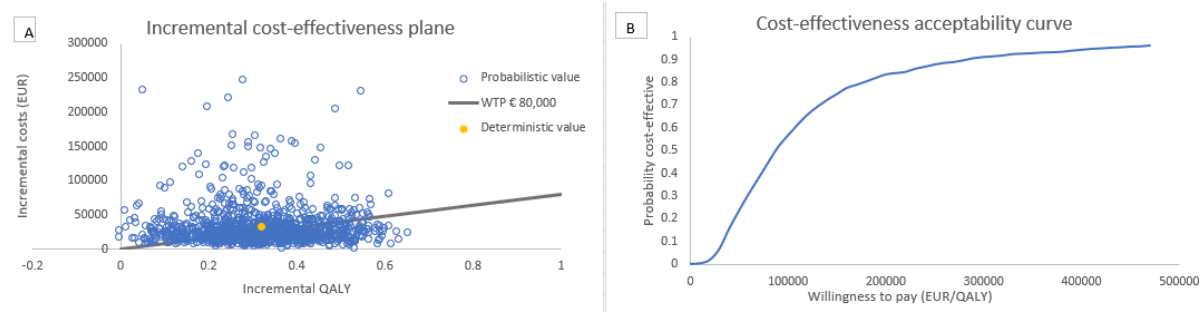


Figure 6: Subgroup male. ICE plane and CEAC scenario 2.

<u>Results subgroup female</u>

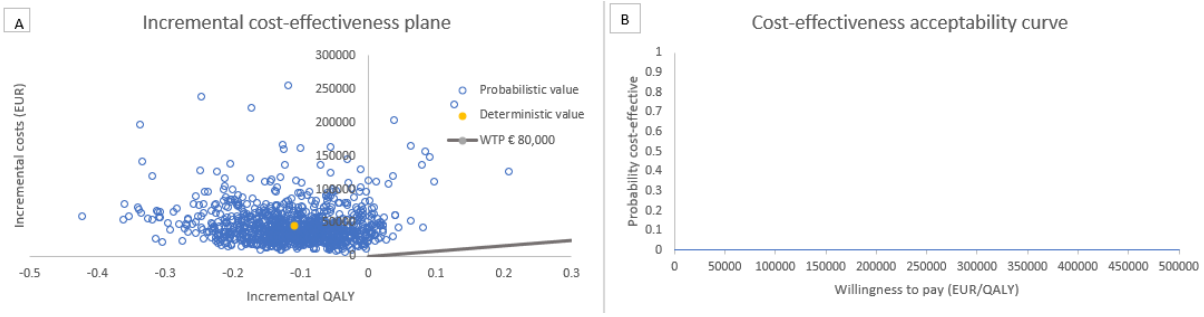


Figure 7: Subgroup female. ICE plane and CEAC scenario 1

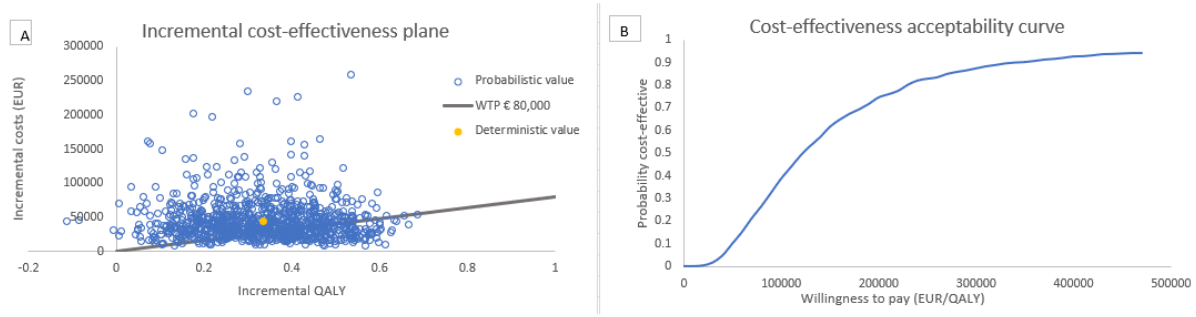


Figure 8: Subgroup female. ICE plane and CEAC scenario 2

Results subgroup age <65 years

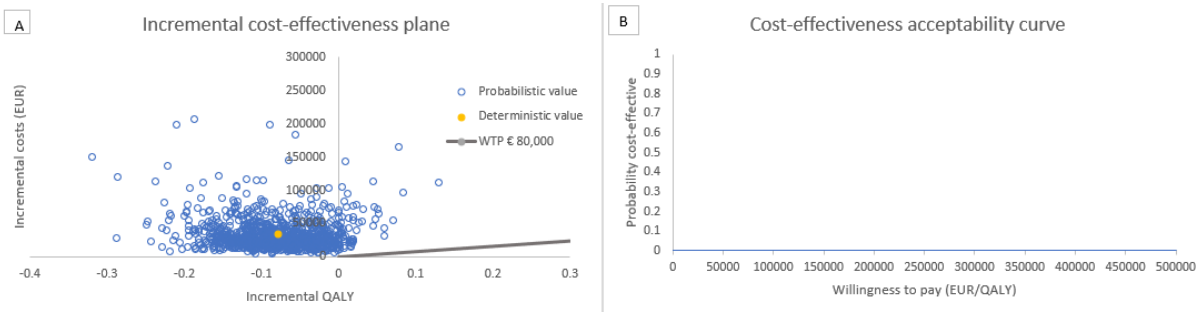


Figure 9: Subgroup age <65 years. ICE plane and CEAC scenario 1

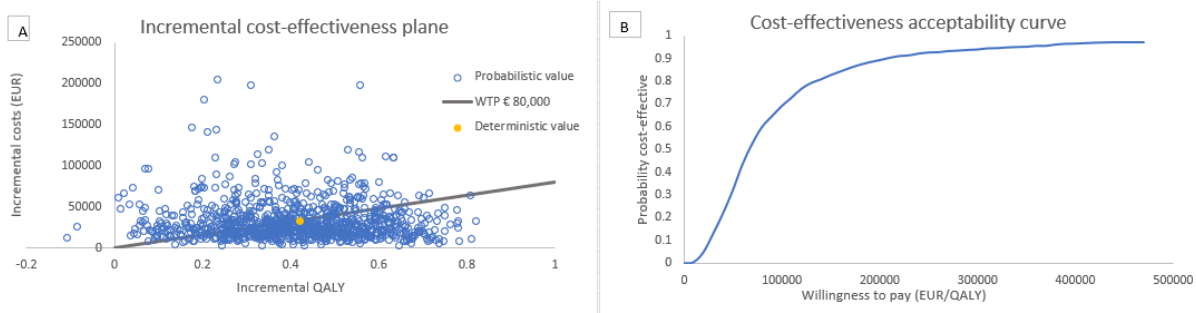


Figure 10: Subgroup age <65 years. ICE plane and CEAC

Results subgroup age ≥65 years

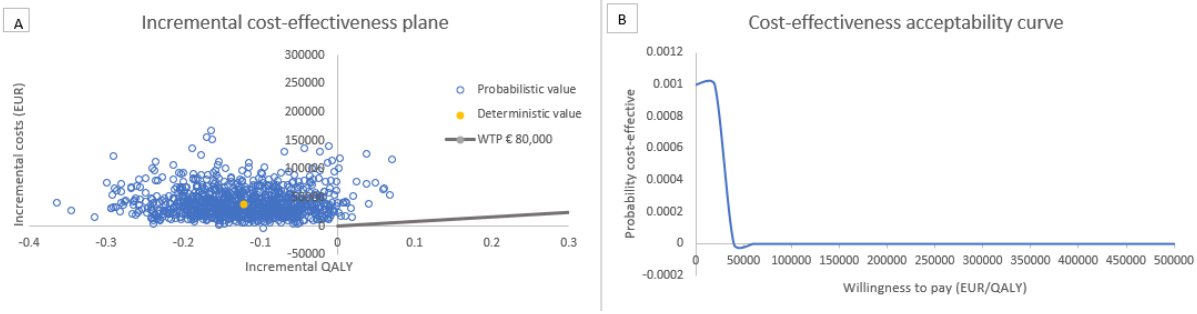


Figure 11: Subgroup age >65 years. ICE plane and CEAC

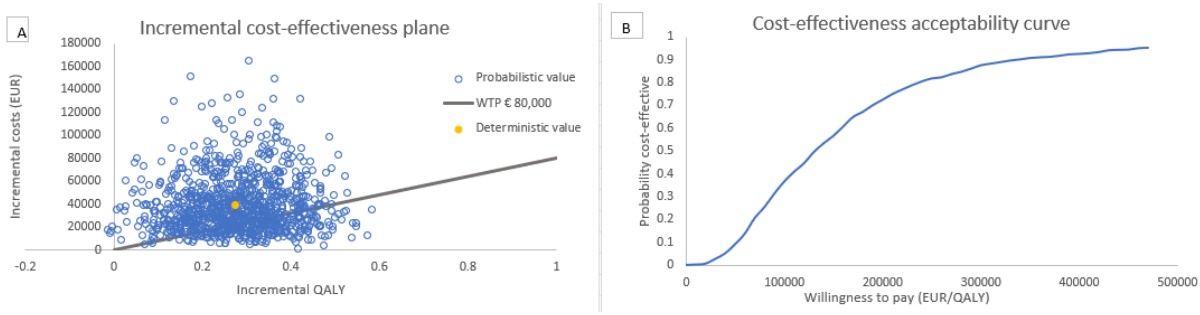


Figure 12: Subgroup age >65 years. ICE plane and CEAC

Results subgroup BMI <25

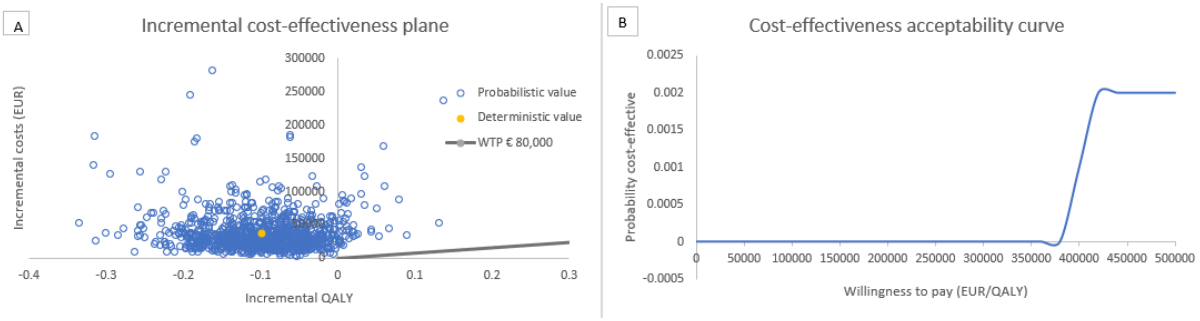


Figure 13: Subgroup BMI <25. ICE plane and CEAC scenario 1

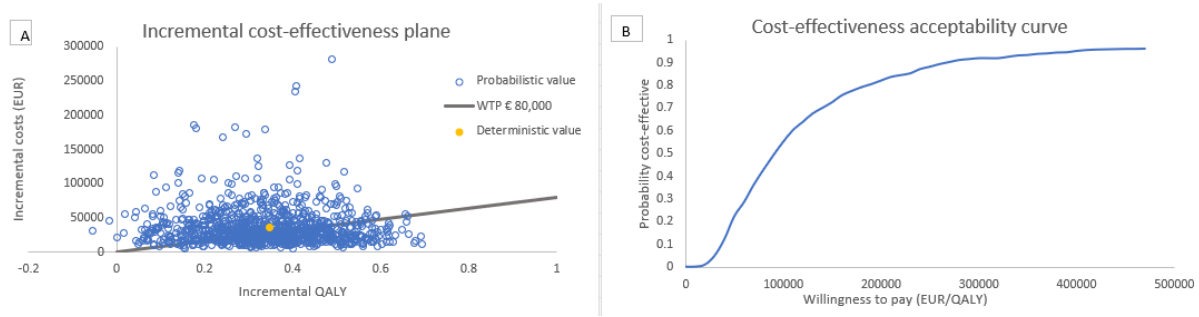


Figure 14: Subgroup BMI <25. ICE plane and CEAC scenario 2

Results subgroup BMI >25

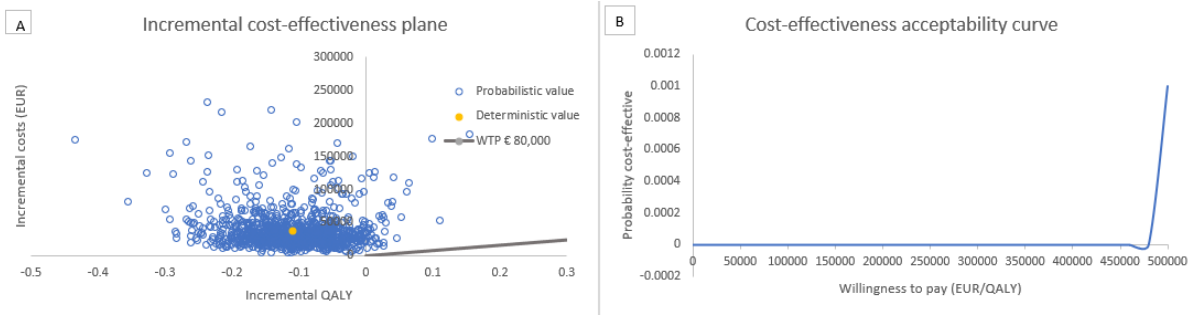


Figure 15: Subgroup BMI >25. ICE plane and CEAC scenario 1

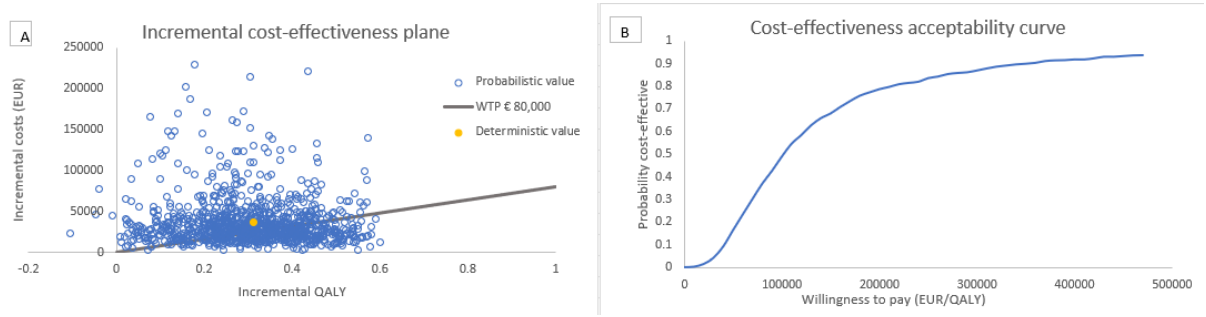


Figure 16: Subgroup BMI >25. ICE plane and CEAC scenario 2

Results subgroup absence of hypertension

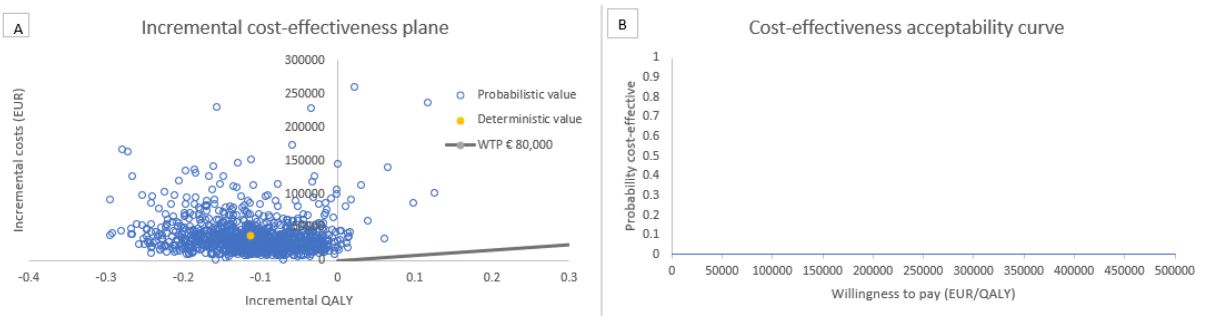


Figure 17: Subgroup absence of hypertension. ICE plane and CEAC scenario 1

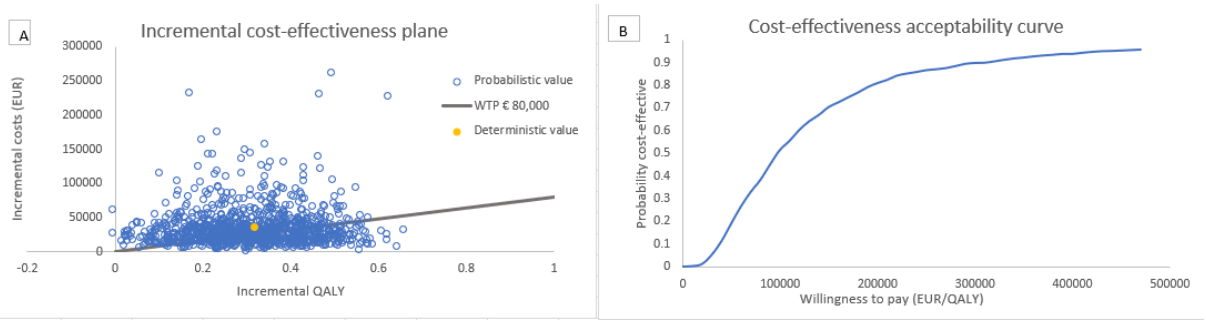


Figure 18: Subgroup absence of hypertension. ICE plane and CEAC scenario 2.

Results subgroup presence of hypertension

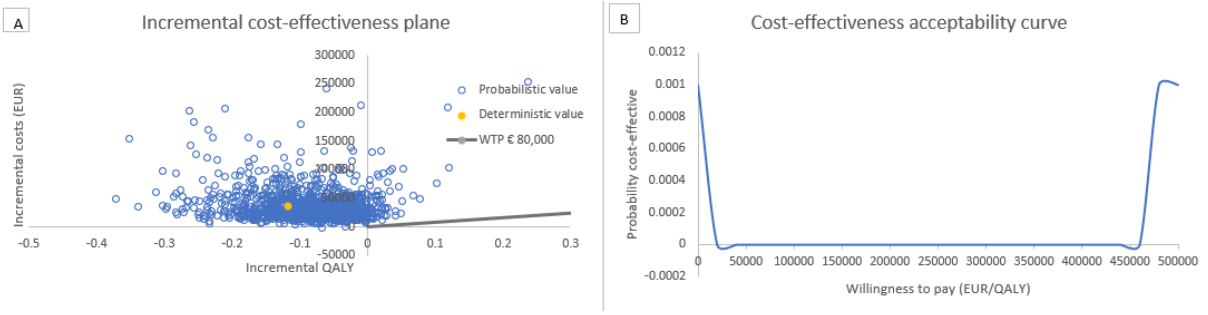


Figure 19: Subgroup presence of hypertension. ICE plane and CEAC scenario 1

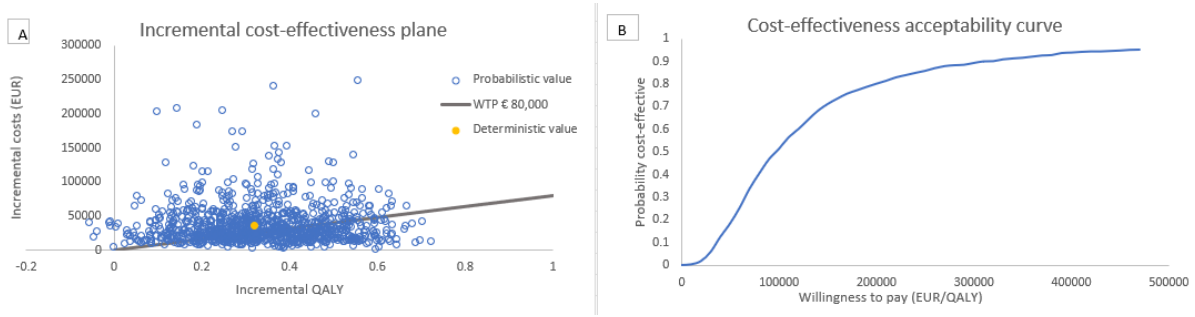


Figure 20: Subgroup presence of hypertension. ICE plane and CEAC scenario 2.