

# Cost-Aware Prediction (CAP): An LLM-Enhanced Machine Learning Pipeline and Decision Support System for Heart Failure Mortality Prediction

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## Abstract

**Objective** Machine learning (ML) predictive models are often developed without considering downstream value trade-offs and clinical interpretability. This paper introduces a *cost-aware prediction* (CAP) framework that combines cost–benefit analysis assisted by *large language model* (LLM) agents to communicate the trade-offs involved in applying ML predictions.

**Materials and Methods** We developed an ML model predicting 1-year mortality in patients with heart failure ( $N = 30,021$ , 22% mortality) to identify those eligible for home care. We then introduced *clinical impact projection* (CIP) curves to visualize important cost dimensions – quality of life and healthcare provider expenses, further divided into treatment and error costs, to assess the clinical consequences of predictions. Finally, we used four LLM agents to generate patient-specific descriptions. The system was evaluated by clinicians for its decision support value.

**Results** The *eXtreme gradient boosting* (XGB) model achieved the best performance, with an *area under the receiver operating characteristic curve* (AUROC) of 0.804 (95% confidence interval (CI) 0.792–0.816), *area under the precision-recall curve* (AUPRC) of 0.529 (95% CI 0.502–0.558) and a Brier score of 0.135 (95% CI 0.130–0.140).

**Discussion** The CIP cost curves provided a *population-level* overview of cost composition across decision thresholds, whereas LLM-generated cost-benefit analysis at *individual patient-levels*. The system was well received according to the evaluation by clinicians. However, feedback emphasizes the need to strengthen the technical accuracy for speculative tasks.

**Conclusion** CAP utilizes LLM agents to integrate ML classifier outcomes and cost-benefit analysis for more transparent and interpretable decision support.

**Keywords:** Cost-Benefit Analysis; Clinical Decision Support Systems; Large Language Models; Heart Failure; Predictive Learning Model

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## Introduction

The use of clinical prediction models based on *artificial intelligence* (AI) holds high promise in medicine, but transition to clinical practice remains challenging. Clinical decision-making seeks to balance available patient information to optimise favourable outcomes and minimise harm. Likewise, *clinical decision support systems* (CDSSs) typically rest

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on multi-objective optimisations as clinical information is computationally combined and translated to finding a local minimum of risk based on the variables included.

Implementation of CDSS ultimately depends on satisfying regulatory requirements and earning clinicians' trust by presenting interpretable AI outputs, communicating the relation between competing objectives, for example, minimising cost while maximising performance and safety<sup>1</sup>.

One method for achieving understandable AI is to present the predicted outcome to the clinician using a decision curve to illustrate benefit relative to risk<sup>2</sup>. A decision curve will describe the theoretical risk prediction for an undesirable outcome in an individual patient in the presence or absence of an intervention recommended by the CDSS and at various levels of probability.

*Heart failure* is a prevalent condition among older individuals<sup>3</sup>, that drives substantial healthcare costs through recurrent hospitalisations, despite the fact that the condition can often successfully be treated at home<sup>4-6</sup>. Here, we report the design of a *machine learning* (ML) prediction model for mortality in patients with severe heart failure, aimed at supporting care-level recommendations – either customised home care as an intervention or hospital readmission as standard care – during periods of worsening health. Beyond predicting 1-year all-cause mortality, we proceed to address downstream consequences such as patient's *quality of life* (QoL) and healthcare resource use through the development of an *interpretable* and *cost-aware* predictive framework, called *cost-aware prediction* (CAP). A semi-quantitative measure is employed to estimate patient-centred costs (e.g. patient outcomes and QoL) and costs for the healthcare provider (e.g. resource allocation and monetary expenses) as examples. The CAP framework illustrates how outcomes can be optimised under varying conditions by balancing these cost dimensions, while delivering high-accuracy predictions and interpretable decision curves. Finally, we attempt to explain the underlying calculations by user-targeted natural language explanations to facilitate interpretation and to support informed clinical decisions.

## Methods

We introduce a decision-support framework, *cost-aware prediction* (CAP) that integrates three components into an interpretable system to support informed decision-making in clinical practice.

### Dataset and prediction outcome

This study includes patients ( $N = 34,139$ ), 18 years and older, with a first in-hospital heart failure diagnosis between January 1, 2017 and December 31, 2023. Diagnoses were registered by codes I110, I130, I132, any I42 or any I50 in any position, according to the International Classification of Diseases (10th revision) (ICD-10). Patient data was collected from a comprehensive database of *electronic health records* (EHRs) covering all hospital-admissions at emergency care providers in the *Region Västra Götaland* (VGR) of Sweden between January 1st 2014 and December 31st 2023 to allow for 3 years of prior history. Sweden has universal healthcare providing low-cost hospital care to all residents. After exclusion of patients with missing information ( $N = 735$ ), and patients who died during the initial hospitalisation ( $N = 3,383$ ), the final cohort consisted of  $N = 30,021$  patients (Fig. 1).

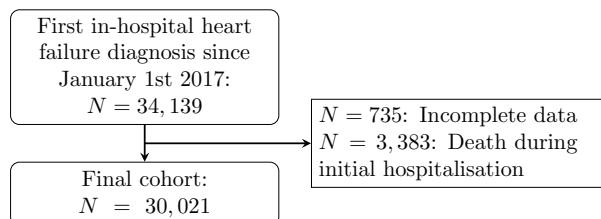


Figure 1: Cohort flow chart indicating selection process

Clinical variables from patient data included: age, sex, body mass index, length of stay, comorbidities along with previous surgeries or interventions within the last 3 years, prescribed drugs within the last year prior to hospitalisation, vital signs and laboratory tests during hospitalisation, and physical mobility extracted from health records within the last 30 days before diagnostic date. For multiple measurements of the same vital sign or laboratory test, the average

value was used for the respective hospitalisation. In total, 75 clinical variables were extracted from EHRs with variable-specific information, such as ICD-10 codes used for comorbidities and Anatomical Therapeutic Chemical (ATC) codes for medications, provided in Supplementary Table S1.

The prediction outcome of the ML model was all-cause mortality within 1 year after discharge after receiving a first heart failure diagnosis during hospitalisation.

### **Component 1: Supervised ML model**

The first component is a supervised ML predictive model that produces a risk score between 0 and 1 for every patient. This score represents the likelihood that an event will occur. To turn this score into a yes-or-no decision, a threshold must be chosen (for example, a decision may be made that patients with a score above 0.7 will be classified as high risk).

### **Component 2: Visualisation of clinical impact factors**

In ML, a classification result can be *true positive* (TP) (a patient correctly predicted to have a high probability of mortality within one year, and who in fact does die within that time), a *false positive* (FP) (a patient predicted to have a high probability of mortality within one year, but who actually survives beyond that time), a *true negative* (TN) (a patient correctly predicted to have a low probability of mortality, and who indeed survives beyond the year), or a *false negative* (FN) (a patient predicted to have a low probability of mortality, but who dies within the year). It is commonly assumed that improved predictive accuracy automatically translates into greater clinical benefits, often without explicitly accounting for the associated clinical impact. This assumption implicitly categorises FPs and FNs as universally “bad”, while treating TPs and TNs as inherently “good”. This view overlooks that in clinical practice, risks can arise even from accurate predictions. Such risks may be influenced by clinical actions triggered by the model’s outputs. Thus, while predictive accuracy remains critical, understanding the downstream impact of ML-based predictions is essential for improving interpretability.

To address this, we introduce the *clinical impact projection* (CIP) curve, where the term *cost* represents the clinical and organisational impact of decisions made based on model predictions. Our design of CIP considers two clinically relevant dimensions:

- QoL cost: typically captures the patient’s lived experience, including aspects relevant to their well-being during care. Lower values indicate better QoL, such as when a patient receives care that is appropriate and minimally intrusive in a familiar environment. A negative QoL cost indicates increased QoL compared to the baseline.
- Healthcare system cost: Reflects the impact on healthcare resources, including hospital bed occupancy, staff workload, and financial expenditures. Lower values indicate more efficient resource utilisation and reduced strain on healthcare systems.

Furthermore, for each dimension, CIP considers two types of costs: clinical treatment cost and classification error cost, reflecting the clinical consequences and classification impact, respectively. More detailed definition and calculation of CIP can be found in Supplementary Section CIP implementation details. Note that users of CIP can define additional cost dimensions and types specific for their context, and that our application represents an example of prioritised costs.

### **Component 3: Cost-benefit analysis using large language model**

Clinicians often find ML model outputs difficult to interpret, particularly when clinical trade-offs must be considered<sup>7-9</sup>. Language models can complement ML decision support by explaining uncertainty and contextualising risks based on patient data and clinical priorities. To address this, the final component of the framework integrates four *large language model* (LLM) agents to support interpretation of model outputs and associated cost–benefit trade-offs. Each agent addresses a key clinical question. The agents operate in a prompt-only mode, prioritising simplicity and traceability over integration with external tools.

**Agent I. How certain is the risk prediction?** Summarises prediction reliability for an individual patient, based on their risk score, decision threshold, and local model performance.

**Agent II. How do I interpret the CIP cost curves?** Explains key contributors to patient-level cost, using treatment and error costs across QoL and healthcare system dimensions.

**Agent III. How can prediction uncertainty be reduced?** Suggests actions (e.g. additional tests, record review) that may improve prediction certainty.

**Agent IV. How can future risks be mitigated?** Provides forward-looking guidance based on predicted outcomes and potential care pathways.

To evaluate the system, we conducted two complementary expert reviews. One clinician, involved in methods development, performed a structured assessment of the outputs for each agent (*clinical development review*), focusing on accuracy and relevance. In addition, two external clinicians (experienced practising specialists in emergency medicine and cardiology, respectively) conducted a *clinical user review*, evaluating interpretability, reliability, and usability of the agents' outputs through structured questions and open-ended feedback (Supplementary Section LLM-agent evaluation details and Supplementary Table S6-S8).

## Implementation of the CAP framework

Here, we will illustrate how to implement this pipeline applying our use case of eligibility for home care programs through 1-year mortality prediction.

### Step 1: ML classification model development

The first step is to develop and select the best performing model based on the ML metric; area under the precision-recall curve and decision threshold based on the best F1 score (Supplementary Section Machine learning model metrics and Machine learning implementation details).

### Step 2: Population-level clinical impact visualisation

Before generating the visualisation (i.e., the CIP cost curves), clinicians must first define the cost structure. Costs need to be specified separately for each type, clinical dimension, and prediction outcome scenario (TP, FP, TN, and FN). In our case study, the costs (ranging from -1 to 1), were defined based on the following assumptions, which represent a *clinical example* to illustrate the CIP/CAP framework:

- Treatment costs: When a patient (either TP or FP) is included in a home care programme, their QoL is expected to improve due to increased comfort, reduced hospitalisations, and greater autonomy. Thus, a negative QoL cost of -1.0 is assigned, which indicates maximum benefits. Simultaneously, healthcare costs decrease due to reduced hospital resource usage, represented as -0.5 in this example. For patients who remain in standard care (TN, FN), both costs are set to 0, as this reflects the default baseline.
- Errors incur additional burden. In our study, a patient incorrectly classified as at high risk of mortality (FP) will receive home care but eventually be rehospitalised, potentially delaying necessary treatment. This results in a moderate QoL penalty of 0.5 and healthcare cost of 0.25. In the case of FN, a high-risk patient is not assigned to home care, potentially leading to a poor end-of-life experience and avoidable strain on the healthcare system. Hence, this is assigned the highest penalty: QoL cost of 1.0 and healthcare cost of 1.0. Correct predictions (TP, TN) incur no error cost.

Given this baseline definition, the full cost matrix (determined by the consensus of clinicians involved in this project) is summarised in Table 1.

Table 1: Assigned quality of life and healthcare costs per outcome scenario

Type	Scenario	QoL cost	Healthcare cost
Treatment	TP	-1.0	-0.5
Treatment	FP	-1.0	-0.5
Treatment	TN	0.0	0.0
Treatment	FN	0.0	0.0
Error	TP	0.0	0.0
Error	FP	0.5	0.25
Error	TN	0.0	0.0
Error	FN	1.0	1.0

FN=false negative. FP=false positive. QoL=quality of life.  
TP=true positive. TN=true negative.

With the definitions of the cost dimensions in place, we compute expected costs at the population level by combining the model's prediction outputs (TP, FP, TN, FN) across a range of decision thresholds from 0 to 1. The CIP cost curves

are then calculated according to Supplementary Section CIP implementation details, which aggregates treatment and error costs across the QoL and healthcare dimensions.

To visualise these components, we introduce a baseline, referred to as the *zero cost curve*, that separates costs (plotted above the baseline) from benefits (plotted below the baseline). Each cost is presented as distinct, colour-coded stacked areas above and below this reference line, respectively, providing an overview of cost composition. The upper boundary of the stacked areas (the silhouette of the curve) represents the net effect, calculated as total cost minus total benefit at each threshold.

### Step 3: Patient-level cost-benefit analysis using four LLM agents

In this step, the system generates a structured clinical cost-benefit analysis tailored to an individual patient. The core prompt components are detailed in Table 2. Detailed prompts are provided in Supplementary Listing S1- S5. We used the state-of-the-art LLM model gpt-4.1-2025-04-14 to implement the agent responses for the prompt queries.

Table 2: Structure of prompts and input dependencies used to construct the four CAP decision support agents

Each column (I–IV) represents a distinct decision support agent. Rows specify the contextual inputs and response dependencies required for each agent.

Type	Prompt	I	II	III	IV
Context	Patient clinical profile	✓	✓	✓	✓
Context	Classifier description	✓			
Context	Classifier decision threshold $r$	✓			
Context	Classifier performance summary near $r$	✓			
Context	Predicted risk score $s$	✓	✓		
Context	Classifier performance summary near $s$	✓			
Context	CIP cost description		✓		
Context	CIP cost coefficients		✓		
Context	Composition of CIP cost curves near $s$		✓		
Context	Response from I		✓	✓	
Context	Response from II				✓
Query	Classification risk analysis	✓			
Query	Clinical cost-benefit analysis		✓		
Query	Classification risk mitigation			✓	
Query	Intervention risk prediction and intervention				✓

CAP=cost-aware prediction. CIP=clinical impact projection. I=How certain is the risk prediction? II=How do I interpret the CIP cost curves? III=How can prediction uncertainty be reduced? IV=How can future risks be mitigated?

## Ethics

Ethical approval of study was granted by the Swedish Ethical Review Authority, through the Ethics Committee of the Umeå University (EPN Reference: DNR 2021-02786).

## Results

### Patient baseline characteristics

The cohort had a median age of 79 years, 45% women and median hospital-admittance 6.1 days at baseline, with a 1-year mortality of 22%. Patients who died were older, more often female and with longer hospital stays (85 years, 48% women, 7.9 days, as compared with 78 years, 44% women and 5.8 days in survivors) as presented in Table 3. Statistical analysis was performed as in Supplementary Section Statistical testing.

### Machine learning performance

We developed various candidate models for the ML classifier, and implementation details are outlined in Supplementary Section Machine learning implementation details and Supplementary Table S2. Figure 2 visualises the *receiver operating characteristic* (ROC) curve, *precision-recall curve* (PRC) and calibration curve for all model candidates. Table 4 reports the bootstrapped estimates of *area under the receiver operating characteristic curve* (AUROC),

Table 3: Baseline characteristics of heart failure cohort - Table continues next page.

Variable	Total	Survived	Deceased within 1 year	p-value
Number of patients	30021	23499	6522	-
<b>Age and sex</b>				
Age (years), median (IQR)	79 (71, 86)	78 (69, 85)	85 (78, 90)	<0.001
Sex				
Women, n (%)	13572 (45)	10432 (44)	3140 (48)	<0.001
BMI ( $\text{kg}/\text{m}^2$ ), median (IQR)	26.5 (23.6, 30.4)	26.8 (23.9, 30.7)	24.7 (21.8, 28.6)	<0.001
<b>Visit information</b>				
ICU stay, n (%)	635 (2.1)	523 (2.2)	112 (1.7)	0.01
ICU days, median (IQR)	5.3 (2.1, 12.0)	5.1 (2.1, 10.4)	7.0 (2.1, 15.9)	0.04
In-hospital days, median (IQR)	6.1 (3.1, 10.9)	5.8 (3.0, 10.0)	7.9 (4.2, 13.7)	<0.001
<b>Comorbidities, n (%)</b>				
CCI, median (IQR)	3 (2, 4)	2 (1, 4)	4 (2, 6)	<0.001
Main heart failure diagnosis	10993 (37)	8565 (36)	2428 (37)	0.25
Alcohol abuse	895 (3.0)	721 (3.1)	174 (2.7)	0.1
Aortic aneurysm	1022 (3.4)	795 (3.4)	227 (3.5)	0.73
Aortic stenosis	2730 (9.1)	1955 (8.3)	775 (12)	<0.001
Asthma	2808 (9.3)	2244 (9.6)	564 (8.6)	0.03
Atrial fibrillation	15485 (52)	11982 (51)	3503 (54)	<0.001
Cancer	6352 (21)	4349 (19)	2003 (31)	<0.001
Cardiomyopathy	2346 (7.8)	2156 (9.2)	190 (2.9)	<0.001
Chronic coronary syndrome	5955 (20)	4546 (19)	1409 (22)	<0.001
Chronic kidney disease	4515 (15)	3007 (13)	1508 (23)	<0.001
COPD	4170 (14)	3016 (13)	1154 (18)	<0.001
Diabetes type 1	1097 (3.6)	861 (3.7)	236 (3.6)	0.89
Diabetes type 2	7598 (25)	5833 (25)	1765 (27)	<0.001
Dyslipidemia	9666 (32)	7672 (33)	1994 (31)	<0.001
Gonarthrosis	2505 (8.3)	1965 (8.4)	540 (8.3)	0.85
Heart failure ICD-10 code I50	28174 (94)	21870 (93)	6304 (97)	<0.001
Hypertension	21130 (70)	16213 (69)	4917 (75)	<0.001
Ischemic stroke	2128 (7.1)	1544 (6.6)	584 (8.9)	<0.001
Leg fracture	2038 (6.8)	1400 (6.0)	638 (9.8)	<0.001
Myocardial infarction	4434 (15)	3572 (15)	862 (13)	<0.001
Obesity	3465 (12)	2938 (12)	527 (8.1)	<0.001
Pulmonary embolism	1140 (3.8)	850 (3.6)	290 (4.5)	<0.001
Substance abuse	1938 (6.5)	1573 (6.7)	365 (5.6)	<0.001
Valvular disease	2873 (9.6)	2271 (9.7)	602 (9.2)	0.3
<b>Previous surgery or interventions, n (%)</b>				
Coronary angioplasty graft	2371 (7.9)	1943 (8.3)	428 (6.6)	<0.001
Coronary artery bypass grafting	1798 (6.0)	1415 (6.0)	383 (5.9)	0.67
Heart transplant	27 (0.1)	22 (0.1)	5 (0.1)	0.86
Pacemaker or defibrillator	2539 (8.5)	1949 (8.3)	590 (9.0)	0.06
Valve replacement	1191 (4.0)	957 (4.1)	234 (3.6)	0.08
<b>Prescribed drugs prior to diagnostic hospitalisation, n (%)</b>				
ACEi	4875 (16)	3977 (17)	898 (14)	<0.001
Antiarrhythmics, class III	789 (2.6)	707 (3.0)	82 (1.3)	<0.001
Angiotensin receptor blockers	3207 (11)	2526 (11)	681 (10)	0.49
ARNI	330 (1.1)	298 (1.3)	32 (0.5)	<0.001
Beta blockers	8947 (30)	7121 (30)	1826 (28)	<0.001
Cardiac glycosides	1893 (6.3)	1486 (6.3)	407 (6.2)	0.83
Cardiac stimulants	673 (2.2)	560 (2.4)	113 (1.7)	<0.001
Loop diuretics	10854 (36)	8003 (34)	2851 (44)	<0.001
Thiazide diuretics	713 (2.4)	547 (2.3)	166 (2.5)	0.33
Diuretics, exclude thiazide	483 (1.6)	319 (1.4)	164 (2.5)	<0.001
MRA	4171 (14)	3322 (14)	849 (13)	0.02
SGLT2 inhibitors	363 (1.2)	311 (1.3)	52 (0.8)	<0.001

ACEi=angiotensin-converting enzyme inhibitors. ARNI=angiotensin receptor neprilysin inhibitors. BMI=body mass index. CCI=Charlson comorbidity index. COPD=chronic obstructive pulmonary disease. GFR=glomerular filtration rate. ICU=intensive care unit. IQR=interquartile range. MRA=mineralocorticoid receptor antagonist. NT-proBNP=N-terminal pro b-type natriuretic peptide. SGLT2=sodium-glucose transport protein 2.

area under the precision-recall curve (AUPRC) and Brier score (BS) for a more robust performance assessment. Boosting machines outperformed simpler models and were well calibrated according to the ideal calibration line. Due to the highest AUPRC out of all candidates, *eXtreme gradient boosting* (XGB) was chosen as the final model

Table 3: Baseline characteristics of heart failure cohort - continued.

Variable	Total	Survived	Deceased within 1 year	p-value
<b>Vital signs, median (IQR)</b>				
Diastolic blood pressure (mmHg)	74 (69, 80)	75 (69, 81)	72 (67, 78)	<0.001
Systolic blood pressure (mmHg)	132 (120, 145)	132 (121, 145)	129 (117, 142)	<0.001
Body temperature (°C)	36.7 (36.4, 36.9)	36.7 (36.5, 36.9)	36.6 (36.4, 36.9)	<0.001
Pulse rate (beats/min)	78 (70, 88)	78 (69, 88)	80 (72, 89)	<0.001
Respiratory rate (breaths/min)	19 (17, 22)	19 (17, 21)	20 (18, 23)	<0.001
Oxygen saturation (%)	96 (94, 97)	96 (94, 97)	95 (93, 96)	<0.001
<b>Laboratories, median (IQR)</b>				
Albumin (34–45 g/L)	33 (29, 36)	33 (30, 36)	31 (27, 34)	<0.001
Bilirubin (5–25 µmol/L)	12 (8, 17)	12 (8, 17)	12 (8, 17)	0.02
Blood urea nitrogen (F/M 8.7–22/9.8–23 mg/dL)	21 (16, 26)	20 (16, 25)	24 (19, 28)	<0.001
C-reactive protein (0–5 mg/L)	19 (5, 61)	16 (5, 58)	30 (10, 71)	<0.001
Creatinine (F/M 45–90/60–105 µmol/L)	88 (72, 107)	86 (71, 105)	93 (73, 114)	<0.001
Ferritin (F/M 5–105/27–400 µg/L)	99 (44, 192)	100 (44, 190)	94 (46, 199)	0.92
Fasting glucose (4–6.9 mmol/L)	6.1 (5.4, 7.0)	6.1 (5.4, 7.0)	6.2 (5.5, 8.0)	0.1
Plasma glucose (4–6.3 mmol/L)	6.8 (6.1, 7.6)	6.8 (6.1, 7.5)	6.9 (6.2, 7.6)	<0.001
Hemoglobin (F/M 117–153/134–170 g/L)	124 (109, 138)	125 (111, 139)	118 (104, 131)	<0.001
Glycated hemoglobin (31–46 mmol/mol)	39 (35, 45)	38 (35, 44)	41 (36, 49)	<0.001
NT-proBNP (0–400 ng/L)	4169 (1870, 8843)	3634 (1641, 7570)	6917 (3190, 14400)	<0.001
Potassium (3.5–4.6 mmol/L)	4.0 (3.8, 4.3)	4.0 (3.8, 4.3)	4.1 (3.8, 4.4)	0.27
Sodium (136–145 mmol/L)	139 (137, 141)	139 (137, 141)	139 (137, 141)	0.1
Alanine transaminase (F/M 0.25–0.60/0.25–0.75 µkat/L)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)	<0.001
Aspartate transaminase (F/M 0.25–0.75/0.25–1.1 µkat/L)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.4 (0.2, 0.6)	<0.001
Troponin I (F/M 0–16/0–35 ng/L)	14 (6, 25)	13 (6, 25)	15 (7, 25)	0.11
Troponin T (0–14 ng/L)	15 (11, 18)	15 (11, 18)	17 (12, 19)	<0.001
Uric acid (F/M 155–400/230–480 µmol/L)	416 (322, 513)	413 (320, 510)	424 (336, 524)	0.31
Estimated GFR (mL/min/1.73m <sup>2</sup> )	57 (45, 70)	59 (47, 71)	50 (40, 63)	<0.001
<b>Physical mobility</b>				
Physical status, median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 2)	<0.001
Pressure wounds, n (%)	3606 (12)	2413 (10)	1193 (18)	<0.001

ACEi=angiotensin-converting enzyme inhibitors. ARNI=angiotensin receptor neprilysin inhibitors. BMI=body mass index. CCI=Charlson comorbidity index. COPD=chronic obstructive pulmonary disease. GFR=glomerular filtration rate. ICU=intensive care unit. IQR=interquartile range. MRA=mineralocorticoid receptor antagonist. NT-proBNP=N-terminal pro b-type natriuretic peptide. SGLT2=sodium-glucose transport protein 2.

for clinical application. The discriminatory capability of XGB resulted in AUROC = 0.804 (95% CI 0.792–0.816) and AUPRC = 0.529 (95% CI 0.502–0.558) with a calibration of BS = 0.135 (95% CI 0.130–0.140). The decision threshold  $t_d = 0.25$  was identified at the maximal F1 score  $F1_{max} = 0.543$  (Supplementary Fig. S2).

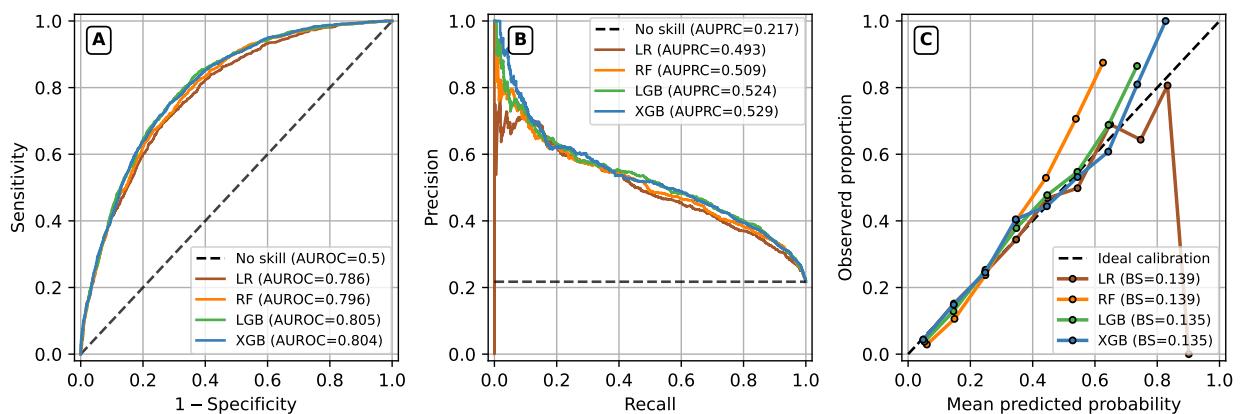


Figure 2: Visual comparison of discriminative and calibration performance of model candidates

Receiver operating characteristic characteristic curve (A), precision-recall curve (B) and calibration curve (C) demonstrate highest predictive performance for gradient boosting machines based on the test set. AUPRC= area under the precision-recall curve. AUROC=area under the receiver operating characteristic curve. BS=Brier score. LGB=light gradient boosting machine. LR=logistic regression. RF=random forest. XGB=eXtreme gradient boosting.

Table 4: Bootstrapped performance comparison of model candidates

AUROC, AUPRC and BS are reported with 95% CIs. Best performances are highlighted in bold.

Model	AUROC	AUPRC	BS
LR	0.786 (0.772-0.799)	0.494 (0.466-0.524)	0.139 (0.134-0.144)
RF	0.797 (0.784-0.809)	0.510 (0.481-0.539)	0.139 (0.135-0.144)
LGB	<b>0.806</b> (0.793-0.818)	0.525 (0.495-0.554)	<b>0.135</b> (0.130-0.140)
XGB	0.804 (0.792-0.816)	<b>0.529</b> (0.502-0.558)	<b>0.135</b> (0.130-0.140)

AUPRC= area under the precision-recall curve. AUROC=area under the receiver operating characteristic curve. BS=Brier score. LGB=light gradient boosting machine. LR=logistic regression. RF=random forest. XGB=eXtreme gradient boosting.

## CIP cost curves

Figure 3 presents the CIP cost curves at different thresholds with a shaded (coloured yellow) risk band, illustrating individual risk, here exemplified for synthetic patient 1. The detailed synthesis process is described in Supplementary Section Synthetic patient generation for LLM prompts. The results from the CIP visualisations provide insights into the clinical impact at the patient-specific predicted risk in comparison to the decision threshold. Moreover, the risk band highlights the relative change in competing costs.

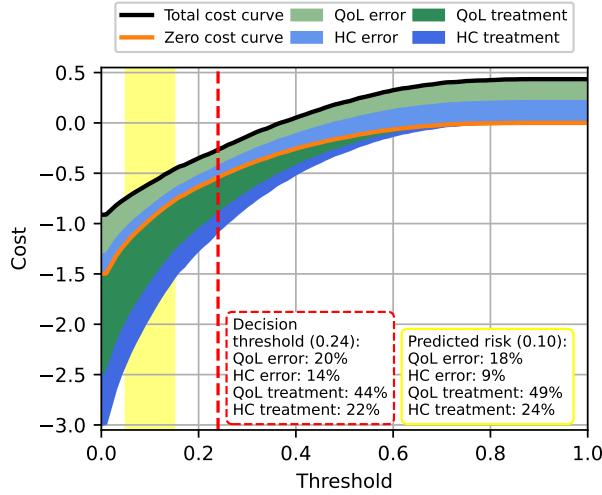


Figure 3: CIP cost curves visualises different cost contributions

CIP cost curves combine the cost curves for prediction error and treatment costs at varying decision thresholds taking different cost dimensions, namely patient's QoL and healthcare system, into account. At the population-level, the stacked cost contributions highlight the clinical impact between potentially competing factors. At the patient-level, CIP visualises the cost-benefit within a risk band (yellow shade) of the patient-specific risk prediction in relation to the decision threshold. CIP=clinical impact projection. HC=health care. QoL=quality of life.

## Evaluation by clinicians

The outcome was evaluated by three clinicians (one clinician for development review and two for user review as in Supplementary Section LLM-agent evaluation details). The review is conducted on 10 synthetic patients (Supplementary Table S5). The clinical development review focused on two key aspects: reliability and clinical accuracy, and it included an inventory of common themes of unsatisfactory quality in its outputs with respect to the specific LLM-agents. A prototype of the CAP framework used for clinical evaluation can be found in Supplementary Fig. S4.

The evaluation revealed clear differences in the perceived reliability and accuracy of the four agent outputs (Likert scale, 1–5). Agent I ("How certain is the risk prediction?") received the highest ratings, with a reliability score of 4.70

and accuracy score of 4.20 across all patients. While generally well-received, the reviewer noted occasional inappropriate terminology and the inclusion of unsupported advice. Agent II ("How do I interpret the CIP cost curves?") was rated as reliable (4.00), but accuracy was lower (2.10), due to speculative statements regarding QoL and healthcare cost consequences. Agent III ("How can prediction uncertainty be reduced?") achieved moderate ratings (reliability 3.60, accuracy 2.30), with qualitative feedback indicating that the advice was sometimes overconfident and partially unsubstantiated. Agent IV ("How can future risks be mitigated?") received the lowest scores (reliability 2.60, accuracy 1.70), with the reviewer describing the guidance as unrealistic and frequently ungrounded.

We categorised the identified themes into 11 categories, which were annotated during the development review. The five most common issues were: (1) incorrect or overreaching medical terminology; (2) overly confident and imperative advice (e.g. use of "shall", "must"); (3) unrealistic, unfeasible, or idealistic recommendations; (4) unasked-for or unsolicited advice; and (5) overbearing or overly prescriptive advice concerning minor details.

The clinical user review was conducted across the same 10 patient cases, with clinicians providing both Likert-scale ratings (1–5) and qualitative comments for each of the CAP components. For risk estimation, the users reported high confidence when using the classifier's risk estimate in combination with the tool, with consistent feedback that the tool enhanced their risk assessment process. The generated risk explanations were generally seen as clear and useful, though in some cases they added little beyond what the risk score already conveyed. The CIP cost curves received mixed feedback. The users found the concept useful for illustrating trade-offs. The tool's uncertainty handling was appreciated, particularly its suggestions for reducing uncertainty, though these were sometimes too generic or incomplete for very complex cases. Importantly, the tool did not create a false sense of reassurance; the user consistently noted it maintained appropriate caution.

## Discussion

Our work focuses on the development of *interpretable* predictive models for 1-year all-cause mortality in heart failure, structured around three central questions. Q1: Why does the model make a positive or negative prediction? Q2: What are the consequences of acting on the model's predictions in clinical care? Q3: How sensitive and robust are these predictions when used in practice?

### European Union AI legal requirements

Importantly, the European Union AI act poses legally binding requirements on transparency, safety, accountability and ethics for development of AI to be applied in health care (Artificial intelligence act<sup>1</sup>). In particular, the EU AI Act requires clear definition, assessment, and governance of risks arising from the output of AI models. CIP addresses this by categorising risks into patient- and healthcare system-related dimensions, thereby aligning with the Act's requirements. Each cost dimension reflects a distinct risk, presented within a structured framework where risks are evaluated based on both technical performance and real-world clinical and economic impact. Notably, the risks here should be read as an relevant example of important considerations in heart failure but may be tailored to the user's needs. Moreover, the evaluation of these costs facilitates effective and transparent communications of risks, as stakeholders can clearly see the trade-offs between different decisions. Thus, the cost evaluation framework will aid in initial risk assessment but also enable the long-term safety, effectiveness, and accountability of the AI system.

### Clinical feedback on LLM-agents

The cost-aware decision guidance, communicated by the LLM-agents, was rated positively and was helpful for assessing future risk. However, the integration of patient-level and population-level information had a steep learning curve for the evaluating clinicians. The generated explanations were generally well-received. The users felt the explanations captured key decision factors and expressed confidence about applying them in practice. There was little concern about content falling outside established guidelines or evidence-based practice, though in complex cases, explanations included unnecessary details or became overly lengthy.

The clinical user review shows that the system was generally well-received for its ability to support risk estimation and explanation, suggesting that the LLM agents are most effective (accurate and helpful) in descriptive and explanatory tasks. However, speculative or forward-looking guidance was unsatisfactory and requires further development. Overall, the clinical user review results suggest the system's strengths lie in supporting risk communication and generating structured clinical explanations.

## Potential applications for policymakers and healthcare financers

Note that although this paper addresses clinicians as stakeholders, it may also be relevant to hospital administrators and policymakers, and can be adjusted according to the selection of included costs. For example, whereas the correctly classified groups, TP and TN, are clinically uncomplicated, the FN illustrate delivery of care that does not contribute to patient value although a costly choice in our model. For comparable conditions, the framework may be useful for policymakers when planning the distribution of hospital beds versus home care.

## Related work

Previous research has successfully demonstrated the application of ML models for prediction of all-cause mortality within 1 year for hospitalised heart failure patients<sup>10–15</sup>. ML models outperformed conventional heart failure risk score models<sup>10,12,13</sup>. Among the various types of AI models, *supervised classification models* are generally the most accurate and reliable for clinical prediction tasks. These ML models follow well-established methods for development, validation, and evaluation, which favour trust in their results in clinical settings. Models of increasing complexity, such as neural networks<sup>16–18</sup> and transformer-based architectures<sup>19,20</sup>, show potential for further gains but typically require larger datasets, may be less robust (high variance), and present greater interpretability challenges. Given the importance of interpretability (Q1) complex model architectures were not prioritised.

Despite advances in model development, the clinical utility of ML models remains limited, and the evaluation of downstream effects of decisions seldom addressed or evaluated (Q2). In clinical practice, risk thresholds for management decisions are rarely well defined but rest on clinical judgement, and the consequences of acting on predictions are often unclear.

Frameworks such as the *misclassification cost term* (MCT)<sup>21</sup> and *decision curve analysis* (DCA)<sup>2</sup> aim to bridge this gap. MCT quantifies optimal thresholds by balancing sensitivity, specificity, prevalence, and predefined costs of FP and FN. However, MCT tightly couples model behaviour to fixed cost terms defined during development, limiting flexibility. DCA visualises net benefit across thresholds, comparing model-guided decisions to treat-none and treat-all strategies<sup>14,22–24</sup>, yet does not break down the cost structure of individual predictions. In contrast, the CIP cost curve provides patient-level cost composition and by illustrating how sensitive these costs are to threshold changes (Q3). DCAs constructed for all model candidates can be found in Supplementary Fig. S3.

To enhance interpretability, LLMs have shown promise in clinical decision support<sup>25–28</sup>, including summarising medical records and assisting with diagnostic reasoning. However, their integration into clinical workflows remains at an early stage. Recent studies have highlighted limitations<sup>29,30</sup>, such as inflexible reasoning, overconfidence in outputs, and susceptibility to errors in complex clinical scenarios. Moreover, LLMs are not inherently reliable for speculative tasks or generating outcomes beyond grounded evidence, as they are prone to hallucinations<sup>25–28</sup>. Evaluations indicate that LLMs may underperform compared with human clinicians, particularly when processing unstructured or nuanced patient data. Findings from our exploratory study are consistent with these observations. Nonetheless, LLM-based approaches hold considerable potential, and further development with rigorous evaluation is warranted.

## Strengths and limitations

Our model is built on a large, comprehensive, and representative regional cohort, ensuring reliable risk mapping, CIP/CAP, and reflecting real-world expectations for healthcare services. It can also simulate outcomes with cost considerations to support threshold-setting in healthcare planning. However, data drift over time necessitates regular updates and validation on contemporary cohorts in the evolving and changing clinical environments. While LLM-based explanations were generally well received, their performance in speculative reasoning and complex patient scenarios remains limited. Further refinement is needed to ensure their safe and reliable clinical use.

## Conclusions

With CAP we propose a three-stage framework:

Firstly, we showed that ML models can effectively predict all-cause mortality within 1 year in a heart failure cohort with a first in-hospital diagnosis, with XGB identified as the best model based on the highest AUPRC.

Secondly, on population-level we theoretically outlined cost matrices including treatment and prediction error costs for two relevant cost dimensions, related to the patient's QoL and the healthcare provider. We then conceptualised CIP to reflect the cost contributions associated with the predictions of the XGB classifier across various risk thresholds expanding traditional ML metrics by accounting for the clinical impact on patient's QoL and healthcare costs.

Thirdly, we integrated LLM agents into the CAP framework to communicate four different aspects of output interpretation, for patient-level decision support.

## Supplementary information

Supplementary information is available in the appendix.

## Contributors

YY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – critical review, commentary & editing. FD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – critical review, commentary & editing. MA: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – critical review, commentary & editing. HS: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – critical review, commentary & editing. CEL: Methodology, Writing – critical review, commentary & editing. ML: Methodology, Writing – critical review, commentary & editing. AR: Resources, Writing – critical review, commentary & editing.

## Declaration of interests

All authors declare no conflict of interest.

## Data sharing

The data and source code are not publicly available but will be made available upon reasonable request after internal review.

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## Supplementary information

**Table S1:** Data collection with detailed information, consisting of outcome for categorical and units for numerical features along with missing percentage, and codes for clinical variables. ACEi=angiotensin-converting enzyme inhibitors. ARNI=angiotensin receptor neprilysin inhibitors. BMI=body mass index. CCI=Charlson comorbidity index. COPD=chronic obstructive pulmonary disease. GFR=glomerular filtration rate. ICU=intensive care unit. MRA=mineralocorticoid receptor antagonist. NT-proBNP=N-terminal pro b-type natriuretic peptide. SGLT2=sodium-glucose transport protein 2. Table continues next page.

Variable	Outcome/Unit	Details (e.g., codes for extraction)	Missing ratio in %
<b>Demographics</b>			
Age	years		0
Sex	0: male, 1: female		0
BMI	kg/m <sup>2</sup>		54.69
<b>Visit information</b>			
ICU stay	0: no, 1: yes		0
ICU days	days		97.88
In-hospital days	days		0
<b>Comorbidities</b>			
CCI	1	CCI was calculated using the comorbidipy package version 0.5.0 with mapping variant charlson and weighting variant se.	0
Main heart failure diagnosis	0: no, 1: yes	Qualifying heart failure diagnosis at primary position	0
Alcohol abuse	0: no, 1: yes	F10	0
Aortic aneurysm	0: no, 1: yes	I71	0
Aortic stenosis	0: no, 1: yes	I350, I352	0
Asthma	0: no, 1: yes	J45	0
Atrial fibrillation	0: no, 1: yes	I48	0
Cancer	0: no, 1: yes	C	0
Cardiomyopathy	0: no, 1: yes	I42, I43	0
Chronic coronary syndrome	0: no, 1: yes	I259	0
Chronic kidney disease	0: no, 1: yes	N18	0
COPD	0: no, 1: yes	J44	0
Diabetes type 1	0: no, 1: yes	E10	0
Diabetes type 2	0: no, 1: yes	E11	0
Dyslipidemia	0: no, 1: yes	E78	0
Gonarthrosis	0: no, 1: yes	M179	0
Heart failure	0: no, 1: yes	I50	0
Hypertension	0: no, 1: yes	I10, I11, I12, I13, I15	0
Ischemic stroke	0: no, 1: yes	I63	0
Leg fracture	0: no, 1: yes	S72, S82, S92	0
Myocardial infarction	0: no, 1: yes	I21	0
Obesity	0: no, 1: yes	E66	0
Pulmonary embolism	0: no, 1: yes	I26	0
Substance abuse	0: no, 1: yes	F11, F12, F13, F14, F15, F16, F17, F18, F19	0
Valvular disease	0: no, 1: yes	I05, I06, I07, I08, I09, I33, I34, I351, I36, I37, I38, I39	0
<b>Previous surgery or interventions</b>			
Coronary angioplasty graft	0: no, 1: yes	Z955	0
Coronary artery bypass grafting	0: no, 1: yes	Z951	0
Heart transplant	0: no, 1: yes	Z941	0
Pacemaker or defibrillator	0: no, 1: yes	Z950	0
Valve replacement	0: no, 1: yes	Z952, Z953, Z954	0
<b>Prescribed drugs prior to diagnostic hospitalisation</b>			
ACEi	0: no, 1: yes	C09AA01, C09AA02, C09AA03, C09AA05, C09AA10	0
Antiarrhythmics, class III	0: no, 1: yes	C01BD	0
Angiotensin receptor blockers	0: no, 1: yes	C09CA01, C09CA03, C09CA06	0
ARNI	0: no, 1: yes	C09DX04	0
Beta blockers	0: no, 1: yes	C07AB02, C07AB07, C07AG02, C07AB12	0
Cardiac glycosides	0: no, 1: yes	C01A	0
Cardiac stimulants	0: no, 1: yes	C01C	0
Loop diuretics	0: no, 1: yes	C03C	0
Thiazide diuretics	0: no, 1: yes	C03A	0
Diuretics, exclude thiazide	0: no, 1: yes	C03B	0
MRA	0: no, 1: yes	C03DA	0

Variable	Outcome/Unit	Details (e.g., codes for extraction)	Missing ratio in %
SGLT2 inhibitors	0: no, 1: yes	A10BK	0
<b>Vital signs</b>			
Diastolic blood pressure	mmHg		5.78
Systolic blood pressure	mmHg		5.11
Body temperature	°C		6.49
Pulse rate	beats/min		5.73
Respiratory rate	breaths/min		15.41
Oxygen saturation	%		6.04
<b>Laboratories</b>			
Albumin	g/L		27.81
Bilirubin	µmol/L		40.82
Blood urea nitrogen	mg/dL		74.06
C-reactive protein	mg/L		8.90
Creatinine	µmol/L		11.95
Ferritin	µg/L		87.42
Fasting glucose	mmol/L		95.93
Plasma glucose	mmol/L		16.39
Hemoglobin	g/L		4.17
Glycated hemoglobin	mmol/mol		86.81
NT-proBNP	ng/L		41.67
Potassium	mmol/L		4.44
Sodium	mmol/L		4.34
Alanine transaminase	µkat/L		44.73
Aspartate transaminase	µkat/L		45.88
Troponin I	ng/L		79.23
Troponin T	ng/L		95.62
Uric acid	µmol/L		97.02
Estimated GFR	mL/min/1.73m <sup>2</sup>	Estimated GFR was calculated using the Lund-Malmö formula LMR18.	11.95
<b>Physical mobility</b>			
Physical status	0: walking without aid, 1: walking with aid, 2: wheelchair, 3: bedrid- den		0
Pressure wounds	0: no, 1: yes		0

## Clinical consequences and interpretations

This section details the clinical consequences of our application. The implications of misclassification require careful consideration. A FP prediction of high mortality risk may lead to premature withdrawal of hospital-based treatment. This risk, while serious, can be mitigated through open-ended treatment plans that allow clinicians to override model-based recommendations based on evolving clinical assessments. Importantly, such flexibility must be maintained, as AI-based models are subject to stricter regulatory requirements than traditional heuristic tools, such as clinical risk scores. Conversely, FNs risk depriving patients of appropriate home-based palliative care, leading to unnecessary aggressive treatment and increased healthcare costs. In this context, the structured explanations generated by the LLM agents can support clinicians in identifying when model outputs warrant closer scrutiny, potentially enhancing the transparency and safety of decision-making. Furthermore, explicit modelling of the costs associated with FPs and FNs provides valuable insight for policymakers and healthcare managers concerned with both clinical outcomes and resource allocation.

## Machine learning model metrics

Developing the ML model involves several technical design choices, including selecting the appropriate model type and tuning its hyperparameters. Model performance is evaluated on a test cohort with real-world electronic health record data, using standard ML metrics such as precision and recall. Precision is defined as the proportion of positive identifications that are actually correct (e.g., the proportion of patients correctly identified as likely to die within a year out of all patients identified as such). Recall is the proportion of actual positives that are correctly identified (e.g., the proportion of patients who died within a year and were correctly identified by the model). We adopted the commonly used ML metric to evaluate and compare the performance of different models: the area under the precision-recall curve with varying thresholds. This metric can be used to automatically select the best overall performing model. To define an operational point of the best classifier for decision-making, the decision threshold is selected as the one that maximises the F1

score across all thresholds, where the F1 score measures the relationship between precision and recall as a single metric calculated as harmonic mean.

### Machine learning implementation details

To predict mortality within 1 year using ML, patient data was divided into 24,016 samples for model training and 6,005 samples for model evaluation stratified for mortality outcome. Four frequently used ML models were employed: logistic regression (LR), random forest (RF), light gradient boosting machine (LGB) and eXtreme gradient boosting (XGB). ML code and models were implemented in Python 3.10.13 with package versions scikit-learn 1.4.0, lightgbm 4.3.0 and xgboost 2.0.0.

Features with more than 80% missing data were removed (Table S1). To address the remaining missingness, features were imputed by the median. As an alternative to median imputation, k-Nearest Neighbors imputation was applied but yielded similar results and was not considered further due to its higher computational cost. Numerical and ordinal features were normalised to [0, 1] and categorical features label encoded.

For all model candidates, hyperparameters were optimised using grid search and stratified 5-fold cross-validation on the training set to ensure equal class distribution in all folds. Models were evaluated by maximising the area under the precision-recall curve to address class imbalance. The optimised hyperparameters for all models are reported in Table S2. The best models were then retrained on the complete training set and evaluated on the unseen test set.

The model's discriminatory capability was assessed using receiver operating characteristic (ROC) curve and precision-recall curve (PRC) with area under ROC curve (AUROC) and area under the precision-recall curve (AUPRC) as threshold-independent metrics to summarise each curve. For the reliability of predicted probabilities, calibration curve and Brier score (BS) were evaluated. The 95% confidence intervals (CI) for AUROC, AUPRC and BS were calculated with bootstrapping (1000 iterations). The best model candidate was identified based on the highest AUPRC over AUROC and the respective decision threshold was determined by the highest F1 score to account for class imbalance in the data.

### CIP implementation details

The purpose of the CIP curve is to visualise how costs are distributed across decision thresholds. Users need to define the relevant cost terms for each clinical dimension (QoL and healthcare provider cost) and cost type. In particular, we consider two cost types in this work,

- Treatment cost ( $C^T$ ): The inherent cost of delivering a given care pathway (for example, hospital-based care or home-based care), independent of prediction accuracy. This is defined relative to a baseline of the standard treatment (for example, hospital-based care).
- Error cost ( $C^E$ ): The additional cost arising from false positive or false negative predictions. This cost is defined relative to the ground truth label.

Let  $p_y(t)$  denote the empirical proportion of patients classified into outcome  $y$  at threshold  $t$ . The expected cost for a given cost type  $\tau$  and dimension  $k$  at threshold  $t$  is defined as:

$$\mathbb{E}(C_k^\tau; t) = \sum_{y \in \{\text{TP, FP, FN, TN}\}} p_y(t) \cdot C_k^\tau(y) \quad (1)$$

where

- $k \in \{1, 2\}$  denotes the cost dimension:  $C_1$  for QoL cost and  $C_2$  for healthcare system cost;
- $\tau \in \{T, E\}$  denotes the cost type: Treatment ( $T$ ) or Error ( $E$ );
- $y \in \{\text{TP, FP, FN, TN}\}$  represents the prediction outcome;
- $t \in [0, 1]$  is the decision threshold applied to the classifier.

The expected cost varies depending on the decision threshold. By systematically evaluating a range of thresholds, we obtain the CIP curve – a population-level overview of the clinical cost implications expressed through these costs.

## Statistical testing

To determine statistical significance ( $p\text{-value} \leq 0.05$ ) between non-events and events (deceased within 1 year), Chi-square test was utilised for categorical features (clinical variables),  $t$ -test for two independent samples for normally distributed numerical features and Mann-Whitney  $U$  rank test for non normally distributed numerical features.

**Table S2:** Hyperparameter optimisation setup using grid search with 5-fold cross-validation. LGB=light gradient boosting machine. LR=logistic regression. RF=random forest. XGB=eXtreme gradient boosting.

Model	Parameter	Search space	Final value
LR	solver	[liblinear, saga]	saga <sup>a</sup>
	penalty	[l1, l2]	l1
	C	[0.1, 1, 10, 100]	1
RF	max_depth	[4, 8, 12]	12
	n_estimators	[100, 300, 500]	500
	min_samples_split	[2, 5, 10]	10
	min_samples_leaf	[1, 2, 4]	1
LGB	max_depth	[4, 8, 12]	12
	n_estimators	[100, 300, 500]	500
	learning_rate	[0.01, 0.1, 0.3]	0.01
	subsample	[0.5, 0.8, 1]	0.5
	colsample_bytree	[0.5, 0.8, 1]	0.5
	reg_alpha	[0, 1, 5]	0
	reg_lambda	[0, 1, 5]	5
	num_leaves	[25, 50]	50
XGB	max_depth	[4, 8, 12]	8
	n_estimators	[100, 300, 500]	500
	learning_rate	[0.01, 0.1, 0.3]	0.01
	subsample	[0.5, 0.8, 1]	0.5
	colsample_bytree	[0.5, 0.8, 1]	0.8
	reg_alpha	[0, 1, 5]	0
	reg_lambda	[0, 1, 5]	0

## Synthetic patient generation for LLM prompts

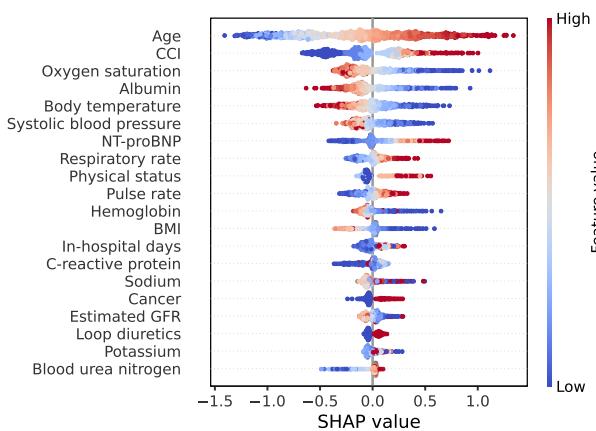
To evaluate the large language model (LLM) agents, synthetic patients were generated to allow for the reproducibility of the prompts used in the cost-aware prediction (CAP) framework. The design of the synthetic patient is limited to 20 features as the synthesis of nearly real-world patients is non-trivial and beyond the scope of this work. Each synthetic patient was reviewed by the clinicians in the project. The 20 features, denoted as the core set  $\mathcal{S}_{\text{core}}$ , include a demographic triplet (age, sex, body mass index) and 17 non-demographic features with the highest contribution to the decision-making by the best classifier. Independent of the assigned contribution, the demographic triplet was included to contextualise the synthetic patient profiles (e.g., sex-dependent laboratory measurements).

The contribution of each feature was evaluated by the SHapley Additive exPlanation (SHAP) method. SHAP values are commonly used to explain the decision process of an ML model by quantifying the average impact of each individual feature on predictions across all possible feature combinations. Figure S1 summarises the SHAP distribution for the top 20 predictive features using XGB which yields the highest AUPRC performance (best classifier). Meanwhile, Table S3 presents the mean SHAP values for all features. To evaluate the competitiveness of XGB when the real patient data was restricted to the core set  $\mathcal{S}_{\text{core}}$ , the classifier was retrained on  $\mathcal{S}_{\text{core}}$  following the previously established implementation pipeline. The hyperparameter tuning was omitted by reusing the hyperparameter setup optimised for  $\mathcal{S}_{\text{complete}}$  (69 features after preprocessing). Figure S2 highlights the comparison of the F1 score across various risk thresholds, demonstrating that the core set  $\mathcal{S}_{\text{core}}$  is competitive with  $\mathcal{S}_{\text{complete}}$  while resulting in a similar decision threshold. Furthermore, Table S4 indicates only a minor performance drop across AUROC, AUPRC and BS.

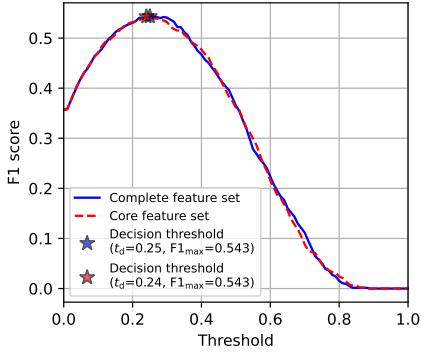
Since the performance comparison has verified that the reduced classifier performs nearly equally well, 10 synthetic patients were generated using the features in  $\mathcal{S}_{\text{core}}$  to utilise their profiles as prompt input for the LLM agents. The 10 synthetic profiles and their respective risk predictions are outlined in Table S5.

**Table S3:** Feature importance of best model (XGB) calculated by mean SHAP values. ACEi=angiotensin-converting enzyme inhibitors. ARNI=angiotensin receptor neprilysin inhibitors. BMI=body mass index. CCI=Charlson comorbidity index. COPD=chronic obstructive pulmonary disease. GFR=glomerular filtration rate. ICU=intensive care unit. MRA=mineralocorticoid receptor antagonist. NT-proBNP=N-terminal pro b-type natriuretic peptide. SGLT2=sodium-glucose transport protein 2. SHAP=SHapley Additive exPlanations. XGB=eXtreme gradient boosting.

Variable	SHAP <sub>mean</sub>	Variable	SHAP <sub>mean</sub>
Age	0.4912	Substance abuse	0.0086
CCI	0.2756	Troponin I	0.0072
Oxygen saturation	0.214	Chronic kidney disease	0.0068
Albumin	0.1795	Alcohol abuse	0.0067
Body temperature	0.1597	Obesity	0.0061
Systolic blood pressure	0.1347	Myocardial infarction	0.0061
NT-proBNP	0.1309	Antiarrhythmics, class III	0.0053
Respiratory rate	0.0905	Leg fracture	0.0049
Physical status	0.0889	Beta blockers	0.0046
Pulse rate	0.0884	Ischemic stroke	0.0045
Hemoglobin	0.0829	Diabetes type 2	0.0044
BMI	0.0759	Hypertension	0.0041
In-hospital days	0.0694	Main heart failure diagnosis	0.004
C-reactive protein	0.0693	ACEi	0.0036
Sodium	0.0646	Chronic coronary syndrome	0.0035
Cancer	0.0617	Valve replacement	0.0019
Estimated GFR	0.0525	Pacemaker or defibrillator	0.0019
Loop diuretics	0.0498	MRA	0.0018
Potassium	0.0463	Cardiac glycosides	0.0015
Blood urea nitrogen	0.0445	Angiotensin receptor blockers	0.0014
Sex	0.0404	Aortic aneurysm	0.0013
Diastolic blood pressure	0.0387	Diuretics, exclude thiazide	0.0013
Pressure wounds	0.0341	Coronary artery bypass grafting	0.0012
Alanine transaminase	0.0312	Thiazide diuretics	0.0011
Creatinine	0.0284	Valvular disease	0.0011
Plasma glucose	0.0251	Diabetes type 1	0.0011
Aspartate transaminase	0.024	ICU stay	0.0009
Bilirubin	0.0205	Heart failure	0.0009
Aortic stenosis	0.0179	Coronary angioplasty graft	0.0009
Dyslipidemia	0.0124	Pulmonary embolism	0.0005
Cardiomyopathy	0.0117	SGLT2 inhibitors	0.0005
Asthma	0.0115	Cardiac stimulants	0.0003
Atrial fibrillation	0.0114	ARNI	0.0002
Gonarthrosis	0.0112	Heart transplant	0.0
COPD	0.0112		



**Figure S1:** Top 20 clinical predictors of best model (XGB) visualised by the SHAP values of each sample and ranked by mean SHAP values. SHAP=SHapley Additive exPlanations. XGB=eXtreme gradient boosting.



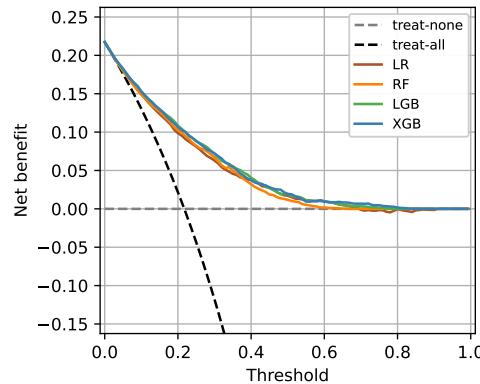
**Figure S2:** Performance comparison of F1 score against various thresholds for the best model (XGB) trained on the original high-dimensional feature space  $\mathcal{S}_{\text{complete}}$  (69 features) versus a core set  $\mathcal{S}_{\text{core}}$  (20 features). Evaluation was performed on the same test set, where each instance was represented by either the complete set or core set of clinical variables. XGB=eXtreme gradient boosting.

**Table S4:** Performance comparison of the XGB model trained and evaluated either on the complete set of clinical variables  $\mathcal{S}_{\text{complete}}$  or the core set of clinical variables  $\mathcal{S}_{\text{core}}$ . AUROC, AUPRC and BS are reported with 95% CI. AUPRC=area under the precision-recall curve. AUROC=area under the receiver operating characteristic curve. BS=Brier score. XGB=eXtreme gradient boosting.

Model	Set	AUROC	AUPRC	BS
XGB	$\mathcal{S}_{\text{complete}}$ (69 features)	0.804 (0.792-0.816)	0.529 (0.502-0.558)	0.135 (0.130-0.140)
XGB	$\mathcal{S}_{\text{core}}$ (20 features)	0.802 (0.789-0.815)	0.520 (0.494-0.549)	0.135 (0.131-0.140)

**Table S5:** Overview of synthetic heart failure patients. The respective risks are predicted by the best classifier (XGB). Values highlighted in grey simulate missing values that are imputed. Alb=albumin. BMI=body mass index. C=cancer. CCI=Charlson comorbidity index. CRP=C-reactive protein. Days=in-hospital days. eGFR=estimated glomerular filtration rate. Hb=hemoglobin. HD=loop diuretics. Id=patient identifier. K=potassium. Na=sodium. NT-proBNP=N-terminal pro b-type natriuretic peptide. O<sub>2</sub>=oxygen saturation. PR=pulse rate. PS=physical status. RR=respiratory rate. SBP=systolic blood pressure. Temp=body temperature. XGB=eXtreme gradient boosting.

Id	Age	Sex	BMI	CCI	O <sub>2</sub>	Alb	Temp	SBP	NT-proBNP	RR	PS	PR	Hb	Days	CRP	Na	C	eGFR	HD	K	Risk
1	86	0	26.5	2	85	37	37.2	161	2424	17	1	75	145	5.1	20	140	0	52	0	4.1	0.010
2	70	0	26.5	1	95	33	36.5	134	252	19	1	81	144	2.1	20	141	0	55	0	4.0	0.025
3	85	0	26.5	2	90	33	37.0	146	4142	19	1	82	151	6.5	22	140	0	56	0	4.2	0.208
4	65	1	26.5	7	92	30	38.2	154	4142	17	0	75	170	5.2	19	141	1	50	1	4.5	0.132
5	79	0	26.5	5	89	33	36.2	145	15241	23	2	79	125	7.1	21	150	1	52	0	4.4	0.62
6	69	1	21.3	1	94	35	36.7	125	4142	22	0	80	156	1.9	25	131	0	49	0	4.1	0.077
7	77	1	26.5	5	88	42	36.2	140	2000	19	1	82	121	6.7	19	135	0	51	0	4.9	0.251
8	75	1	26.5	5	91	38	36.8	147	17450	19	2	82	135	1.6	26	141	0	48	1	3.8	0.182
9	84	1	26.5	4	90	34	37.5	153	6123	17	1	78	154	2.4	23	138	1	47	0	4.4	0.157
10	72	0	25.2	4	92	32	37.1	134	1124	17	0	79	141	4.7	27	131	0	58	0	4.1	0.144



**Figure S3:** Clinical applicability of all model candidates at different risk thresholds illustrated by decision curve analysis from the test set. LGB=light gradient boosting machine. LR=logistic regression. RF=random forest. XGB=eXtreme gradient boosting.

## Listing S1 How certain is the risk prediction? (Agent I) for synthetic patient 1

```

1## System
2You are a highly precise medical AI assistant with expertise in clinical decision support.
3Your primary role is to assist clinicians in **objectively** conducting cost-benefit analysis of AI-based risk models** for patient care.
4
5Your responses must be:
6- Clear and structured.
7- Supported by patient condition and numerical reasoning.
8- Informative and specific about the patient.
9
10Avoid:
11- Subjective or vague recommendations.
12- Stating obvious facts.
13
14 =====
15
16## Patient profile (the most important consideration factors):
17The patient is diagnosed with heart failure (ICD-10 I50) in-hospital for the first time.
18This is the patient info: {"age_at_index": 86, "sex": 0, "BMI": 26.5, "CCI": 2, "saturation": 85, "albumin": 37, "body_temperature": 37.2, "blood_pressure_systolic": 161, "nt_probpn": 2424, "respiratory_rate": 17, "physical_status": 1, "pulse_rate": 75, "hemoglobin": 145, "inhospital_days": 5.1, "c_reactive_protein": 20, "sodium": 140, "cancer": 0, "eGFR": 52, "HD": 0, "potassium": 4.1}
19This is the context info of the clinical variables:
20 - sex maps to (0: male, 1: female)
21 - physical_status maps to (0: walking without aid, 1: walking with aid, 2: wheelchair, 3: bedridden) within the last 30 days
22 - HD to a prescription of loop diuretics within the last year
23 - Mapping of ICD-10 codes (feature: code): (Cancer: C)
24 - Mapping of ATC code levels (feature: code): (HD: C03C)
25
26## Mortality prediction classifier:
27You are provided with a machine learning classifier that predicts one-year mortality in heart failure patients.
28The classifier assigns each patient a likelihood of mortality. A threshold determines the final classification:
29- If the probability > threshold, the patient is classified as high risk (positive).
30- If the probability < threshold, the patient is classified as low risk (negative).
31This classifier is evaluated at multiple thresholds, yielding different values for true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN).
32The optimal threshold is 0.24.
33The classifier demonstrates the following performance across decision thresholds around 0.24: {0.19: {'TP': 1044, 'FP': 1594, 'TN': 3106, 'FN': 261}, 0.2: {'TP': 1022, 'FP': 1515, 'TN': 3185, 'FN': 283}, 0.21: {'TP': 1000, 'FP': 1445, 'TN': 3255, 'FN': 305}, 0.22: {'TP': 983, 'FP': 1382, 'TN': 3318, 'FN': 322}, 0.23: {'TP': 963, 'FP': 1302, 'TN': 3398, 'FN': 342}, 0.24: {'TP': 940, 'FP': 1215, 'TN': 3485, 'FN': 365}, 0.25: {'TP': 917, 'FP': 1158, 'TN': 3542, 'FN': 388}, 0.26: {'TP': 886, 'FP': 1097, 'TN': 3603, 'FN': 419}, 0.27: {'TP': 866, 'FP': 1042, 'TN': 3658, 'FN': 439}, 0.28: {'TP': 841, 'FP': 978, 'TN': 3722, 'FN': 464}, 0.29: {'TP': 815, 'FP': 926, 'TN': 3774, 'FN': 490}}
34The predicted score is 0.1.
35The classifier demonstrates the following performance across decision thresholds around 0.1: {0.05: {'TP': 1279, 'FP': 3518, 'TN': 1182, 'FN': 26}, 0.06: {'TP': 1268, 'FP': 3304, 'TN': 1396, 'FN': 37}, 0.07: {'TP': 1255, 'FP': 3121, 'TN': 1579, 'FN': 50}, 0.08: {'TP': 1243, 'FP': 2952, 'TN': 1748, 'FN': 62}, 0.09: {'TP': 1230, 'FP': 2779, 'TN': 1921, 'FN': 75}, 0.1: {'TP': 1213, 'FP': 2631, 'TN': 2069, 'FN': 92}, 0.11: {'TP': 1202, 'FP': 2472, 'TN': 2228, 'FN': 103}, 0.12: {'TP': 1185, 'FP': 2329, 'TN': 2371, 'FN': 120}, 0.13: {'TP': 1153, 'FP': 2208, 'TN': 2492, 'FN': 152}, 0.14: {'TP': 1136, 'FP': 2090, 'TN': 2610, 'FN': 169}, 0.15: {'TP': 1112, 'FP': 1967, 'TN': 2733, 'FN': 193}}
36
37 ## Task
38Analyze the patient's profile.
39Given the classifier's decision threshold of 0.24 and that the predicted score for the patient is 0.1,
40evaluate the reliability of the predicted classification for this specific patient, referencing the classifier's performance across neighboring thresholds.
41
42The output should be specific to the patient, excluding generic summaries of the classifier.
43Make a comprehensive and supportive analysis for the clinician considering all factors.
44Be critical. Do not speculate about potential downstream treatments.
45
46The output should be formatted as a JSON instance that conforms to the JSON schema below.
47
48As an example, for the schema {"properties": {"foo": {"title": "Foo", "description": "a list of strings", "type": "array", "items": {"type": "string"}}, "required": ["foo"]}}
49the object {"foo": ["bar", "baz"]} is a well-formatted instance of the schema. The object {"properties": {"foo": ["bar", "baz"]}} is not well-formatted.
50
51Here is the output schema:
52```
53{"$defs": {"MisclassificationConsequence": {"properties": {"type": {"description": "The potential misclassification type relevant to the patient.", "enum": ["False Positive", "False Negative", "Type", "string"], "likelihood": {"description": "Likelihood of this misclassification for this patient at or near the threshold.", "enum": ["High", "Moderate", "Low"], "title": "Likelihood", "type": "string"}, "rationale": {"description": "Numerical and clinical reasoning behind this likelihood estimate.", "title": "Rationale", "type": "string"}, "concerns": {"description": "The concerns of the potential prediction error. Return No concerns if none. Be critical.", "title": "Concerns", "type": "string"}, "patient_profile_analysis": {"description": "The analysis of patient clinical profile in terms of mortality within 1 year.", "title": "Patient Profile Analysis", "type": "string"}, "required": ["type", "likelihood", "rationale", "concerns", "patient_profile_analysis"], "title": "MisclassificationConsequence", "type": "object"}, "predicted_score": {"description": "Patient-specific predictive risk profiling", "properties": {"predicted_score": {"description": "Predicted mortality probability for the patient.", "title": "Predicted Score", "type": "number"}, "applied_threshold": {"description": "Threshold used for classification decision.", "title": "Applied Threshold", "type": "number"}, "predicted_label_by_classifier": {"description": "Classifier outcome for the patient.", "enum": ["High Risk", "Low Risk"], "title": "Predicted Label By Classifier", "type": "string"}, "predicted_label_after_analysis": {"description": "Predicted outcome for the patient after risk analysis.", "enum": ["High Risk", "Low Risk"], "title": "Predicted Label After Analysis", "type": "string"}, "misclassification_analysis": {"anyOf": [{"$ref": "#/$defs/MisclassificationConsequence"}, {"type": "null"}]}, "default": null, "description": "Analysis of the most likely misclassification risk and its consequence for this patient."}, "overall_assessment": {"description": "Objective interpretation of the classifier's decision in the patient's context.", "title": "Overall Assessment", "type": "string"}, "required": ["predicted_score", "applied_threshold", "predicted_label_by_classifier", "predicted_label_after_analysis", "overall_assessment"]}}
```

## **Listing S2 How do I interpret the CIP cost curves? (Agent II) for synthetic patient 1?**

```

1## System
2You are a highly precise medical AI assistant with expertise in clinical decision support.
3Your primary role is to assist clinicians in **objectively conducting cost-benefit analysis of AI-based risk models** for patient care.
4
5Your responses must be:
6- Clear and structured.
7- Supported by patient condition and numerical reasoning.
8- Informative and specific about the patient.
9
10Avoid:
11- Subjective or vague recommendations.
12- Stating obvious facts.
13
14=====
15
16## Patient profile (the most important consideration factors):
17The patient is diagnosed with heart failure (ICD-10 ISO) in-hospital for the first time.
18This is the patient info: {"age_at_index": 86, "sex": 0, "BMI": 26.5, "CCI": 2, "saturation": 85, "albumin": 37, "body_temperature": 37.2, "blood_pressure_systolic": 161, "nt_proBNP": 2424, "respiratory_rate": 17, "physical_status": 1, "pulse_rate": 75, "hemoglobin": 145, "inhospital_days": 5.1, "c_reactive_protein": 20, "sodium": 140, "cancer": 0, "eGFR": 52, "HD": 0, "potassium": 4.1}
19This is the context info of the clinical variables:
20 - sex maps to 0: male, 1: female
21 - physical_status maps to 0: walking without aid, 1: walking with aid, 2: wheelchair, 3: bedridden) within the last 30 days
22 - HD to a prescription of loop diuretics within the last year
23 - Mapping of ICD-10 codes (feature: code): (Cancer: C)
24 - Mapping of ATC code levels (feature: code): (HD: C03C)
25
26## Patient risk analysis
27{"predicted_score":0.1,"applied_threshold":0.24,"predicted_label_by_classifier": "Low Risk","predicted_label_after_analysis": "Low Risk","misclassification_analysis": {"type": "False Negative", "likelihood": "Low", "rationale": "The patient's predicted score (0.1) is substantially below the applied threshold (0.24). At the nearest evaluated threshold (0.1), the classifier demonstrates a sensitivity (TPR) of 92.9% (1213/1305) and a false negative rate of 7.1% (92/1305). As the threshold increases toward 0.24, the number of false negatives rises (from 92 at 0.1 to 365 at 0.24), but the predicted score is distinctly below both thresholds, making misclassification as false negative (wrongly classified as low risk) unlikely for this patient.", "concerns": "No concerns. The large separation between the patient's score and the threshold, coupled with strong sensitivity at and below this threshold, suggests very low probability of significant underestimation of risk for this patient.", "patient_profile_analysis": "This 86-year-old male with systolic hypertension, low oxygen saturation (85%), moderately impaired kidney function (eGFR 52), and an elevated NT-proBNP (2424) presents with a frail clinical profile (dependent on walking aids, CCI 2), all of which are adverse prognosticators for 1-year mortality in heart failure. However, based purely on the model's output, he is classified as low risk. This suggests that despite clinical frailty, the input features weighted by the model yield a low predicted risk, possibly due to preserved albumin and hemodynamic stability.", "overall_assessment": "The classifier's decision to label this patient as low risk is reliable given the substantial margin between the patient's predicted score (0.1) and the operational threshold (0.24). The classifier's sensitivity at and below this point is high, minimizing the risk of false negatives. Re-analysis in the context of the patient's adverse risk factors supports heightened clinical vigilance, but the model's output at this margin does not indicate likely misclassification."}}
28
29## Clinical costs:
30If the classifier assigns a positive label, the patient will be enrolled in a home care program.
31If the classifier assigns a negative label, the patient will continue with regular hospital-based care.
321. **Treatment cost (treatment)** is the cost due to the home care program (positive treatment) associated with each outcome.
322. **Prediction error costs (error)** is the additional cost when the classifier makes an incorrect prediction (a misclassification).
33
34Home care programs generally improve quality of life due to increased comfort and convenience, while also reducing healthcare costs.
35For this patient, clinical outcomes are expected to remain similar to those achieved through regular hospital visits.
36However, if the patient is a false positive (FP), they may initially be assigned to home care but require urgent hospital readmission, leading to increased costs for both quality of life and healthcare.
37Conversely, if the patient is a false negative (FN), they will continue with standard hospital care, which may reduce their quality of life due to unnecessary hospital visits and impose higher costs on the healthcare system.
38
39To reflect these considerations, clinicians defined the cost weights to be: {'QoL Treatment': {'TP': -1.0, 'FP': -1.0, 'TN': 0.0, 'FN': 0.0}, 'QoL Prediction Error': {'TP': 0.0, 'FP': 0.5, 'TN': 0.0, 'FN': 1.0}, 'Healthcare Treatment': {'TP': -0.5, 'FP': -0.5, 'TN': 0.0, 'FN': 0.0}, 'Healthcare Prediction Error': {'TP': 0.0, 'FP': 0.25, 'TN': 0.0, 'FN': 1.0}}
40
41The total cost around the predicted score 0.1: {0.05: {'Cost Total': -0.75}, 0.06: {'Cost Total': -0.72}, 0.07: {'Cost Total': -0.69}, 0.08: {'Cost Total': -0.66}, 0.09: {'Cost Total': -0.63}, 0.1: {'Cost Total': -0.6}, 0.11: {'Cost Total': -0.57}, 0.12: {'Cost Total': -0.55}, 0.13: {'Cost Total': -0.51}, 0.14: {'Cost Total': -0.49}, 0.15: {'Cost Total': -0.46}}
42Cost composition is calculated as: abs(cost)/sum(abs(all costs at this threshold)); sign is either positive cost (negative impact) or negative cost (benefit).
43QoL treatment cost around the predicted score 0.1: {0.05: {'composition': 0.49, 'sign': 'neg.'}, 0.06: {'composition': 0.49, 'sign': 'neg.'}, 0.07: {'composition': 0.49, 'sign': 'neg.'}, 0.08: {'composition': 0.49, 'sign': 'neg.'}, 0.09: {'composition': 0.49, 'sign': 'neg.'}, 0.1: {'composition': 0.49, 'sign': 'neg.'}, 0.11: {'composition': 0.49, 'sign': 'neg.'}, 0.12: {'composition': 0.48, 'sign': 'neg.'}, 0.13: {'composition': 0.48, 'sign': 'neg.'}, 0.14: {'composition': 0.48, 'sign': 'neg.'}, 0.15: {'composition': 0.48, 'sign': 'neg.'}}
44Healthcare treatment cost around the predicted score 0.1: {0.05: {'composition': 0.24, 'sign': 'neg.'}, 0.06: {'composition': 0.24, 'sign': 'neg.'}, 0.07: {'composition': 0.24, 'sign': 'neg.'}, 0.08: {'composition': 0.24, 'sign': 'neg.'}, 0.09: {'composition': 0.24, 'sign': 'neg.'}, 0.1: {'composition': 0.24, 'sign': 'neg.'}, 0.11: {'composition': 0.24, 'sign': 'neg.'}, 0.12: {'composition': 0.24, 'sign': 'neg.'}, 0.13: {'composition': 0.24, 'sign': 'neg.'}, 0.14: {'composition': 0.24, 'sign': 'neg.'}, 0.15: {'composition': 0.24, 'sign': 'neg.'}}
45QoL error cost around the predicted score 0.1: {0.05: {'composition': 0.18, 'sign': 'pos.'}, 0.06: {'composition': 0.18, 'sign': 'pos.'}, 0.07: {'composition': 0.18, 'sign': 'pos.'}, 0.08: {'composition': 0.18, 'sign': 'pos.'}, 0.09: {'composition': 0.18, 'sign': 'pos.'}, 0.1: {'composition': 0.18, 'sign': 'pos.'}, 0.11: {'composition': 0.18, 'sign': 'pos.'}, 0.12: {'composition': 0.18, 'sign': 'pos.'}, 0.13: {'composition': 0.18, 'sign': 'pos.'}, 0.14: {'composition': 0.18, 'sign': 'pos.'}, 0.15: {'composition': 0.18, 'sign': 'pos.'}}
46Healthcare error cost around the predicted score 0.1: {0.05: {'composition': 0.09, 'sign': 'pos.'}, 0.06: {'composition': 0.09, 'sign': 'pos.'}, 0.07: {'composition': 0.09, 'sign': 'pos.'}, 0.08: {'composition': 0.09, 'sign': 'pos.'}, 0.09: {'composition': 0.09, 'sign': 'pos.'}, 0.1: {'composition': 0.09, 'sign': 'pos.'}, 0.11: {'composition': 0.09, 'sign': 'pos.'}, 0.12: {'composition': 0.1, 'sign': 'pos.'}, 0.13: {'composition': 0.1, 'sign': 'pos.'}, 0.14: {'composition': 0.1, 'sign': 'pos.'}, 0.15: {'composition': 0.11, 'sign': 'pos.'}}
47
48## Task
49Analyze the patient's profile. Given the patient profile, conduct cost-benefit analysis for this specific patient, referencing different types of costs across neighboring thresholds.
50
51The output should be specific to the patient, excluding generic summaries of the cost.
52Make a comprehensive and supportive analysis for the clinician considering all factors.
53Be critical.
54
55The output should be formatted as a JSON instance that conforms to the JSON schema below.
56
57As an example, for the schema {"properties": {"foo": {"title": "Foo", "description": "a list of strings", "type": "array", "items": {"type": "string"}}, "required": ["foo"]}, the object {"foo": ["bar", "baz"]} is a well-formatted instance of the schema. The object {"properties": {"foo": ["bar", "baz"]}} is not well-formatted.
58
59Here is the output schema:
60
61
62
63{"$defs": {"CostSummary": {"properties": {"threshold": {"description": "Threshold being evaluated.", "title": "Threshold", "type": "number"}, "total_cost": {"description": "Combined cost across all categories.", "title": "Total Cost", "type": "number"}, "qol_treatment_cost": {"description": "QoL treatment cost. Include a single float only, no calculation.", "title": "QoL Treatment Cost", "type": "number"}, "healthcare_treatment_cost": {"description": "Healthcare treatment cost. Include a single float only, no calculation.", "title": "Healthcare Treatment Cost", "type": "number"}, "qol_error_cost": {"description": "QoL error cost. Include a single float only, no calculation.", "title": "QoL Error Cost", "type": "number"}, "healthcare_error_cost": {"description": "Healthcare error cost. Include a single float only, no calculation.", "title": "Healthcare Error Cost", "type": "number"}, "required": ["threshold", "total_cost", "qol_treatment_cost", "healthcare_treatment_cost", "qol_error_cost", "healthcare_error_cost"], "title": "CostSummary", "type": "object"}, "description": {"cost": {"cost": "Cost landscape interpretation", "properties": {"predicted_score": {"description": "Predicted risk score for the patient.", "title": "Predicted Score", "type": "number"}, "decision_label": {"description": "Classifier's decision label at this score.", "title": "Decision Label", "type": "string"}, "main_risk_factors": {"description": "Key clinical variables influencing cost.", "title": "Main Risk Factors", "type": "string"}, "cost_composition_at_predicted_score": {"$ref": "#/defs/CostSummary", "description": "Cost breakdown at current score threshold."}, "lowest_cost_threshold": {"description": "Threshold with lowest total cost nearby.", "title": "Lowest Cost Threshold", "type": "number"}, "summary": {"description": "Concise plain-language interpretation of the cost-benefit tradeoff for this patient, closing with an actionable recommendation if applicable. Any cost composition should be reported on percentage.", "title": "Summary", "type": "string"}}, "required": ["predicted_score", "decision_label", "main_risk_factors", "cost_composition_at_predicted_score", "lowest_cost_threshold", "summary"]}}, "type": "array", "items": {"type": "string"}}, "required": ["foo"]}}
```

### Listing S3 How can prediction uncertainty be reduced? (Agent III) for synthetic patient 1

```

1## System
2You are a highly precise medical AI assistant with expertise in clinical decision support.
3Your primary role is to assist clinicians in **objectively** conducting cost-benefit analysis of AI-based risk models** for patient care.
4
5Your responses must be:
6- Clear and structured.
7- Supported by patient condition and numerical reasoning.
8- Informative and specific about the patient.
9
10Avoid:
11- Subjective or vague recommendations.
12- Stating obvious facts.
13
14=====
15
16## Patient profile (the most important consideration factors):
17The patient is diagnosed with heart failure (ICD-10 I50) in-hospital for the first time.
18This is the patient info: {"age_at_index": 86, "sex": 0, "BMI": 26.5, "CCI": 2, "saturation": 85, "albumin": 37, "body_temperature": 37.2, "blood_pressure_systolic": 161, "nt_probpn": 2424, "respiratory_rate": 17, "physical_status": 1, "pulse_rate": 75, "hemoglobin": 145, "inhospital_days": 5.1, "c_reactive_protein": 20, "sodium": 140, "cancer": 0, "eGFR": 52, "HD": 0, "potassium": 4.1}
19This is the context info of the clinical variables:
20 - sex maps to (0: male, 1: female)
21 - physical_status maps to (0: walking without aid, 1: walking with aid, 2: wheelchair, 3: bedridden) within the last 30 days
22 - HD to a prescription of loop diuretics within the last year
23 - Mapping of ICD-10 codes (feature: code): (Cancer: C)
24 - Mapping of ATC code levels (feature: code): (HD: C03C)
25
26## Patient risk analysis
27("predicted_score":0.1,"applied_threshold":0.24,"predicted_label_by_classifier":"Low Risk","predicted_label_after_analysis":"Low Risk","misclassification_analysis":{"type":"False Negative","likelihood":"Low","rationale":"The patient's predicted score (0.1) is substantially below the applied threshold (0.24). At the nearest evaluated threshold (0.1), the classifier demonstrates a sensitivity (TPR) of 92.9% (1213/1305) and a false negative rate of 7.1% (92/1305). As the threshold increases toward 0.24, the number of false negatives rises (from 92 at 0.1 to 365 at 0.24), but the predicted score is distinctly below both thresholds, making misclassification as false negative (wrongly classified as low risk) unlikely for this patient.", "concerns":"No concerns. The large separation between the patient's score and the threshold, coupled with strong sensitivity at and below this threshold, suggests very low probability of significant underestimation of risk for this patient.", "patient_profile_analysis":"This 86-year-old male with systolic hypertension, low oxygen saturation (85%), moderately impaired kidney function (eGFR ~ 52), and an elevated NT-proBNP (2424) presents with a frail clinical profile (dependent on walking aids, CCI 2), all of which are adverse prognosticators for 1-year mortality in heart failure. However, based purely on the model's output, he is classified as low risk. This suggests that despite clinical frailty, the input features weighted by the model yield a low predicted risk, possibly due to preserved albumin and hemodynamic stability."}, "overall_assessment":"The classifier's decision to label this patient as low risk is reliable given the substantial margin between the patient's predicted score (0.1) and the operational threshold (0.24). The classifier's sensitivity at and below this point is high, minimizing the risk of false negatives. Re-analysis in the context of the patient's adverse risk factors supports heightened clinical vigilance, but the model's output at this margin does not indicate likely misclassification."}
28
29## Task
30Analyze the patient's profile and the risk analysis of the classifier.
31Suggest action points for the clinicians in order to make more confident predictions of this patient.
32
33The output should be specific to the patient, excluding generic summaries of the classifier.
34Be critical.
35
36The output should be formatted as a JSON instance that conforms to the JSON schema below.
37
38As an example, for the schema {"properties": {"foo": {"title": "Foo", "description": "a list of strings", "type": "array", "items": {"type": "string"}}, "required": ["foo"]}}
39the object {"foo": ["bar", "baz"]} is a well-formatted instance of the schema. The object {"properties": {"foo": ["bar", "baz"]}} is not well-formatted.
40
41Here is the output schema:
42```
43("${$defs": {"ActionPointC": {"properties": {"action": {"description": "Concise title describing the recommended clinical action.", "title": "Action", "type": "string"}, "rationale": {"description": "Justification for the recommendation, grounded in the patient's data and clinical reasoning.", "title": "Rationale", "type": "string"}, "suggested_tests_or_data": {"anyOf": [{"items": {"type": "string", "type": "array", "type": "null"}}, {"description": "Specific measurements, labs, or assessments that would increase confidence in the risk estimate.", "title": "Suggested Tests Or Data"}, {"expected_clinical_value": {"anyOf": [{"type": "string", "type": "null"}]}}, {"default": null, "description": "Explanation of how the new data would contribute to the clinical interpretation or next steps.", "title": "Expected Clinical Value"}], "type": "array", "title": "ActionPointC", "type": "object"}, "description": "Uncertainty reduction strategy", "properties": {"patient_id": {"anyOf": [{"type": "string"}, {"type": "null"}]}, "predicted_score": {"type": "string"}, {"type": "null"}}, "default": null, "description": "Unique patient identifier; optional if anonymized.", "title": "Patient Id"}, "predicted_score": {"type": "number"}, "threshold": {"description": "Risk threshold applied to convert the predicted score into a binary risk classification.", "title": "Threshold", "type": "number"}, "predicted_label": {"description": "Final binary risk label for the patient after classifier analysis (e.g., 'High Risk').", "title": "Predicted Label", "type": "string"}, "misclassification_risk": {"description": "Characterization of the risk that the model output is a false positive or false negative.", "title": "Misclassification Risk", "type": "string"}, "action_points": {"description": "A list of patient-specific, clinically actionable steps to improve risk stratification confidence in decreasing order of priority.", "title": "Action Points", "type": "array"}, "final_recommendations": {"description": "A concise, action-oriented summary of the recommended steps to mitigate risk. Avoid over-generalization as the summarized actions should be practical to follow. Use a considerate, not a commanding tone.", "title": "Final Recommendations", "type": "string"}}, "required": ["predicted_score", "threshold", "predicted_label", "misclassification_risk", "action_points", "final_recommendations"]}}, "44```

```

#### **Listing S4 How can future risks be mitigated? (Agent IV) for synthetic patient 1**

```

1## System
2You are a highly precise medical AI assistant with expertise in clinical decision support.
3Your primary role is to assist clinicians in **objectively conducting cost-benefit analysis of AI-based risk models** for patient care.
4
5Your responses must be:
6- Clear and structured.
7- Supported by patient condition and numerical reasoning.
8- Informative and specific about the patient.
9
10Avoid:
11- Subjective or vague recommendations.
12- Stating obvious facts.
13
14=====
15
16## Patient profile (the most important consideration factors):
17The patient is diagnosed with heart failure (ICD-10 I50) in-hospital for the first time.
18This is the patient info: {"age_at_index": 86, "sex": 0, "BMI": 26.5, "CCI": 2, "saturation": 85, "albumin": 37, "body_temperature": 37.2, "blood_pressure_systolic": 161, "nt_probpnn": 2424, "respiratory_rate": 17, "physical_status": 1, "pulse_rate": 75, "hemoglobin": 145, "inhospital_days": 5.1, "c_reactive_protein": 20, "sodium": 140, "cancer": 0, "eGFR": 52, "HD": 0, "potassium": 4.1}
19This is the context info of the clinical variables:
20 - sex maps to (0: male, 1: female)
21 - physical_status maps to (0: walking without aid, 1: walking with aid, 2: wheelchair, 3: bedridden) within the last 30 days
22 - HD to a prescription of loop diuretics within the last year
23 - Mapping of ICD-10 codes (feature: code): (Cancer: C)
24 - Mapping of ATC code levels (feature: code): (HD: C03C)
25
26## Patient cost-benefit analysis
27{"predicted_score":0.1,"decision_label": "Low Risk", "main_risk_factors": "Advanced age (86), male sex, first heart failure admission, marked hypoxemia (saturation 85%), moderate renal impairment (eGFR 52), elevated NT-proBNP (2424), markedly elevated systolic blood pressure (161), CCI 2, requirement for walking aids. These factors raise baseline risk, but preserved albumin, stable vital signs, and no malignancy or dialysis moderate this assessment.", "cost_composition_at_predicted_score": {"threshold": 0.1, "total_cost": -0.6, "qol_treatment_cost": -0.294, "healthcare_treatment_cost": -0.144, "qol_error_cost": 0.108, "healthcare_error_cost": 0.064}, "lowest_cost_threshold": 0.05, "summary": "At the patient's predicted score of 0.1, total cost is -0.6, indicating moderate net benefit. The largest contribution (49%) is quality-of-life (QoL) benefit from avoided unnecessary treatment, followed by a 24% healthcare cost saving. Positive costs from potential quality-of-life (18%) and healthcare (9%) prediction errors persist, reflecting some risk of reduced patient QoL and increased system cost if risk is underestimated. The lowest total cost (-0.75) is just above the prediction (threshold 0.05), driven similarly by treatment-related benefits. Given the substantial margin between score and the decision threshold, the classifier is unlikely to misclassify this patient as low risk despite significant clinical frailty. Actionable recommendation: The model output for this patient offers a cost-favorable, low-risk decision, but clinical vigilance is advised due to the patient's frailty. If risk margin narrows or health status changes, consider sensitivity analysis at marginally lower thresholds."}
28
29## Task
30Analyze the patient's clinical profile in conjunction with the model-based cost-benefit assessment of treatment deployment.
31Based on this analysis, and assuming treatment is initiated, identify targeted action points to mitigate patient-specific risks.
32The goal is not to reduce mortality risks, but to warn the clinicians about treatment-specific risks.
33
34Recommendations must be tailored to this individual patient's clinical context. Avoid any generic or model-wide summaries.
35
36The output should be formatted as a JSON instance that conforms to the JSON schema below.
37
38As an example, for the schema {"properties": {"foo": {"title": "Foo", "description": "a list of strings", "type": "array", "items": {"type": "string"}}, "required": ["foo"]}, the object {"foo": ["bar", "baz"]} is a well-formatted instance of the schema. The object {"properties": {"foo": ["bar", "baz"]}} is not well-formatted.
39
40
41Here is the output schema:
42```
43{"$defs": {"ActionPointD": {"properties": {"action": {"description": "Concise description of the proposed action.", "title": "Action", "type": "string"}, "rationale": {"description": "Justification based on treatment-specific clinical profile and treatment context.", "title": "Rationale", "type": "string"}, "monitoring_or_tests": {"anyOf": [{"items": {"type": "string"}, "type": "array"}, {"type": "null"}]}, "description": "Tests or assessments required for this action.", "title": "Monitoring Or Tests"}, "mitigation_goal": {"anyOf": [{"type": "string"}, {"type": "null"}]}, "default": null, "description": "What this action aims to reduce or prevent.", "title": "Mitigation Goal"}, "cost": {"type": "object"}, "CostComponent": {"properties": {"name": {"description": "Component of the cost model, e.g., 'quality of life', 'healthcare cost'."}, "title": "Name", "type": "string"}, "value": {"description": "Relative contribution to total cost (range: 0.0 to 1.0).", "title": "Value", "type": "number"}, "explanation": {"description": "Explanation of how this cost component is impacted for this patient.", "title": "Explanation", "type": "string"}}, "RiskFactor": {"properties": {"name": {"description": "Specific clinical variable contributing to risk.", "title": "Name", "type": "string"}, "value": {"description": "Observed value or category for the patient.", "title": "Value", "type": "string"}, "interpretation": {"description": "Patient-specific implication of the value.", "title": "Interpretation", "type": "string"}, "required": ["name", "value", "interpretation"], "title": "RiskFactor", "type": "object"}, "description": "Cost-aware decision guidance.", "properties": {"patient_id": {"anyOf": [{"type": "string"}, {"type": "null"}]}, "default": null, "description": "Optional identifier if used in patient record systems."}, "title": "Patient Id"}, "predicted_score": {"description": "Predicted mortality or risk score from the AI model.", "title": "Predicted Score", "type": "number"}, "decision_label": {"description": "AI model's final decision label for the patient (e.g., 'High Risk').", "title": "Decision Label", "type": "string"}, "main_risk_factors": {"description": "Key clinical features contributing to risk classification.", "items": {"$ref": "#$defs/RiskFactor"}, "title": "Main Risk Factors", "type": "array"}, "cost_summary": {"description": "Breakdown of cost components at the predicted score.", "items": {"$ref": "#$defs/CostComponent"}, "title": "Cost Summary", "type": "array"}, "treatment_plan": {"description": "Treatment or care program being deployed based on decision (e.g., home care).", "title": "Treatment Plan", "type": "string"}, "recommended_actions_post_treatment": {"description": "Targeted clinical actions to mitigate future risk ensuring beneficial post-treatment.", "items": {"$ref": "#$defs/ActionPointD"}, "title": "Recommended Actions Post Treatment", "type": "array"}, "final_recommendations": {"description": "A concise, action-oriented summary of the recommended steps to mitigate future risk with beneficial post-treatment. Use a considerate, not a commanding tone.", "title": "Final Recommendations", "type": "string"}, "required": ["predicted_score", "decision_label", "main_risk_factors", "cost_summary", "treatment_plan", "recommended_actions_post_treatment", "final_recommendations"]}}
44```

```

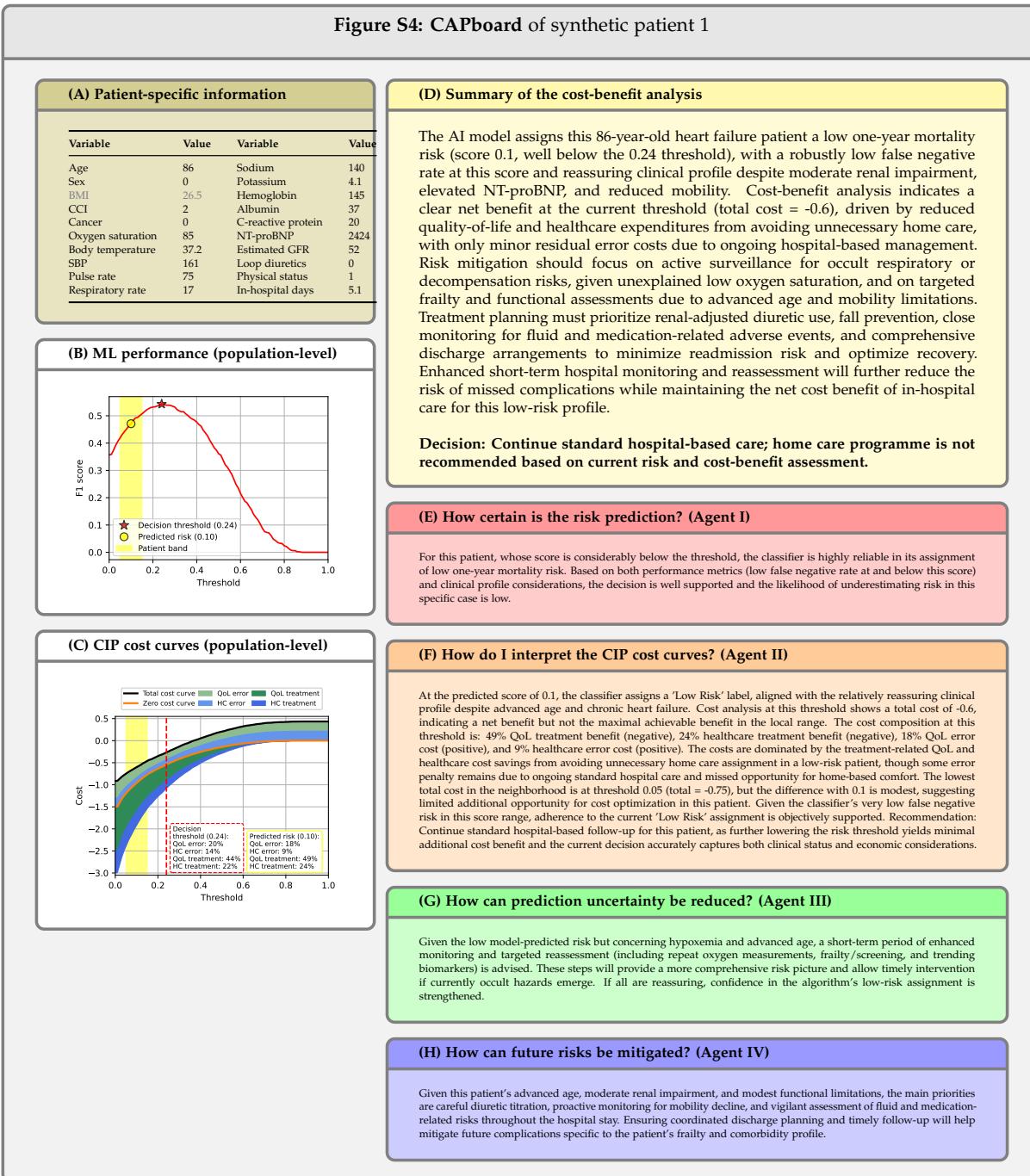
## Listing S5 Summary of the cost-benefit analysis for synthetic patient 1

```

1## System
2You are a highly precise medical AI assistant with expertise in clinical decision support.
3Your primary role is to assist clinicians in **objectively** conducting cost-benefit analysis of AI-based risk models** for patient care.
4Your responses must be:
5- Clear and structured.
6- Supported by patient condition and numerical reasoning.
7- Informative and specific about the patient.
8Avoid:
9- Subjective or vague recommendations.
10- Stating obvious facts.
11
12=====
13
14## Task:
15Summarize the following outcomes for patient to a clinician.
16Focus on a cost benefit analysis.
17Do not add or alter existing information or results. Be concise.
18
19## Outcome risk analysis:
20("predicted_score":0.1,"applied_threshold":0.24,"predicted_label_by_classifier":"Low Risk","predicted_label_after_analysis":"Low
   → Risk","misclassification_analysis":{"type":"False Negative","likelihood":"Low","rationale":"The patient's predicted score (0.1) is substantially below the applied
   → threshold (0.24). At the nearest evaluated threshold (0.1), the classifier demonstrates a sensitivity (TPR) of 92.9% (1213/1305) and a false negative rate of 7.1%
   → (92/1305). As the threshold increases toward 0.24, the number of false negatives rises (from 92 at 0.1 to 365 at 0.24), but the predicted score is distinctly below both
   → thresholds, making misclassification as false negative (wrongly classified as low risk) unlikely for this patient.", "concerns":"No concerns. The large separation between
   → the patient's score and the threshold, coupled with strong sensitivity at and below this threshold, suggests very low probability of significant underestimation of risk
   → for this patient.", "patient_profile_analysis":"This 86-year-old male with systolic hypertension, low oxygen saturation (85%), moderately impaired kidney function (eGFR
   → 52), and an elevated NT-proBNP (2424) presents with a frail clinical profile (dependent on walking aids, CCI 2), all of which are adverse prognosticators for 1-year
   → mortality in heart failure. However, based purely on the model's output, he is classified as low risk. This suggests that despite clinical frailty, the input features
   → weighted by the model yield a low predicted risk, possibly due to preserved albumin and hemodynamic stability.", "overall_assessment":"The classifier's decision to label
   → this patient as low risk is reliable given the substantial margin between the patient's predicted score (0.1) and the operational threshold (0.24). The classifier's
   → sensitivity at and below this point is high, minimizing the risk of false negatives. Re-analysis in the context of the patient's adverse risk factors supports heightened
   → clinical vigilance, but the model's output at this margin does not indicate likely misclassification."}
21
22## Outcome cost interpretation:
23("predicted_score":0.1,"decision_label":"Low Risk","main_risk_factors":"Advanced age (86), male sex, first heart failure admission, marked hypoxemia (saturation 85%),
   → moderate renal impairment (eGFR 52), elevated NT-proBNP (2424), markedly elevated systolic blood pressure (161), CCI 2, requirement for walking aids. These factors raise
   → baseline risk, but preserved albumin, stable vital signs, and no malignancy or dialysis moderate this
   → assessment.", "cost_composition_at_predicted_score": {"threshold":0.1,"total_cost":-0.6,"gol_treatment_cost":-0.294,"healthcare_treatment_cost":-0.144,"gol_error_cost":0.108,
   → "healthcare_error_cost":-0.054}, "lowest_cost_threshold":0.05,"summary":"At the patient's predicted score of 0.1, total cost is -0.6, indicating moderate net benefit. The
   → largest contribution (49%) is quality-of-life (QoL) benefit from avoided unnecessary treatment, followed by a 24% healthcare cost saving. Positive costs from potential
   → quality-of-life (18%) and healthcare (9%) prediction errors persist, reflecting some risk of reduced patient QoL and increased system cost if risk is underestimated. The
   → lowest total cost (-0.75) is just above the prediction (threshold 0.05), driven similarly by treatment-related benefits. Given the substantial margin between score and
   → the decision threshold, the classifier is unlikely to misclassify this patient as low risk despite significant clinical frailty. Actionable recommendation: The model
   → output for this patient offers a cost-favorable, low-risk decision, but clinical vigilance is advised due to the patient's frailty. If risk margin narrows or health
   → status changes, consider sensitivity analysis at marginally lower thresholds."}
24
25## Outcome risk mitigation:
26("patient_id":null,"predicted_score":0.1,"threshold":0.24,"predicted_label":"Low Risk","misclassification_risk":"Low likelihood of false negative; model sensitivity at or
   → below threshold is high, but clinical profile carries adverse prognosticators (age, chronic kidney disease, frailty, hypoxemia), creating a potential disconnect between
   → model estimation and bedside judgment.", "action_points": [{"action": "Reassess and trend oxygenation status", "rationale": "Patient's oxygen saturation is critically low at
   → 85%, which is an independent predictor of mortality in heart failure and may not be fully weighted in the current model. Confirming the accuracy and trend of oxygenation
   → (including consideration for arterial blood gases) would help to clarify acute severity and residual risk.", "suggested_tests_or_data": ["Repeat pulse oximetry at
   → intervals", "Arterial blood gas (ABG) analysis", "Assessment for supplemental oxygen requirement"], "expected_clinical_value": "Better characterization of hypoxic burden
   → and response to therapies could identify evolving decompensation risk not fully captured by the AI model."}, {"action": "Review for acute or subacute decompensation not
   → captured in model inputs", "rationale": "Low albumin, high NT-proBNP, and moderate eGFR reduction suggest systemic stress and possible subacute organ
   → decompensation-features that may prompt under-recognition of short-term risk by the model.", "suggested_tests_or_data": ["Repeat NT-proBNP after diuresis", "Daily weight
   → trend", "Input/output balance analysis", "Assess for new symptoms (e.g., confusion, increasing fatigue, reduced urine output)", "expected_clinical_value": "Detection of
   → worsening congestion or evolving multi-organ dysfunction, which may necessitate reclassification of risk and timely intervention."}, {"action": "Obtain frailty and
   → functional status reassessment", "rationale": "Current classification reflects 'walking with aids', but frailty scores (e.g., Clinical Frailty Scale, handgrip strength)
   → provide nuanced prognostic information in elderly heart failure patients and may be missed by structured data-fed models.", "suggested_tests_or_data": ["Clinical Frailty
   → Scale evaluation", "Timed Up-and-Go test"], "expected_clinical_value": "Improved individual mortality risk stratification and more accurate tailoring of follow-up
   → intensity."}, {"action": "Request external validation of PI (prediction index) or cross-model consensus in this subgroup", "rationale": "Given advanced age and frail clinical
   → characteristics, models trained on broader populations may exhibit calibration drift. Benchmarking this patient's risk by applying a second validated model (e.g., MAGIC,
   → Seattle HF Model) could confirm or refine the risk estimate.", "suggested_tests_or_data": ["Calculate MAGIC score", "Re-run risk with a heart failure-specific external
   → tool"], "expected_clinical_value": "Mitigates single-model bias and boosts confidence in the classification, especially in a high-variability clinical
   → subgroup."}], "final_recommendations": "Although AI model output suggests low risk, key adverse clinical features warrant caution. Trend the patient's oxygenation and early
   → decompensation markers, reassess frailty using standardized tools, and consider second-model risk estimation. These targeted steps will strengthen individualized
   → prognostication beyond the current classifier."}
27
28## Outcome cost benefit recommendation:
29("patient_id":null,"predicted_score":0.1,"decision_label":"Low Risk","main_risk_factors": [{"name": "Age", "value": "86", "interpretation": "Advanced age increases frailty and
   → susceptibility to treatment side effects."}, {"name": "Oxygen Saturation", "value": "85%", "interpretation": "Marked hypoxemia may complicate diuretic therapy or exacerbate
   → underlying respiratory limitations."}, {"name": "Systolic Blood Pressure", "value": "161 mmHg", "interpretation": "Elevated blood pressure could increase risk of hypotension
   → with heart failure therapies."}, {"name": "NT-proBNP", "value": "2424", "interpretation": "Significant cardiac strain/volume overload, necessitating cautious fluid
   → management."}, {"name": "eGFR", "value": "52", "interpretation": "Stage 3 chronic kidney disease; increased risk for electrolyte disturbances and drug accumulation with heart
   → failure treatment."}, {"name": "Physical Status", "value": "Walking with aids", "interpretation": "Functional limitation, increasing fall risk especially if overt diuresis or
   → hypotension occurs."}], "cost_summary": [{"name": "QoL Treatment Benefit", "value": "0.49", "explanation": "Major gain from avoiding unnecessary or overly aggressive interventions
   → in a frail, elderly patient."}, {"name": "Healthcare Treatment Cost", "value": "0.24", "explanation": "Reduced direct cost due to optimized, likely less intensive therapy in a
   → patient categorized as low risk."}, {"name": "QoL Prediction Error Cost", "value": "0.18", "explanation": "Residual risk to quality of life if risk is underestimated and expected
   → recovery is not achieved or subclinical decompensation occurs."}, {"name": "Healthcare Prediction Error Cost", "value": "0.09", "explanation": "Potential for unexpected
   → healthcare utilization if disease trajectory does not follow predicted low-risk path."}], "treatment_plan": [{"name": "Initiation of standard evidence-based heart failure therapy
   → (likely including diuretics, afterload reduction, and monitoring in step-down or outpatient setting)"}, {"name": "recommended_actions_post_treatment": [{"action": "Monitor for
   → hypovolemia and electrolyte disturbances within 48 hours post-treatment initiation."}, {"name": "monitoring_or_tests": ["Daily weights", "Serum sodium, potassium, creatinine", "Assessment for
   → orthostatic symptoms"]}], "mitigation_goal": "Mimimize risk of acute kidney injury, metabolic disturbances, and iatrogenic falls."}, {"name": "Assess for symptomatic
   → hypotension at least daily during medication titration."}, {"name": "Markedly elevated systolic blood pressure at baseline alongside frailty may lead to overshooting
   → target blood pressures with antihypertensives or up-titration of heart failure medications."}, {"name": "monitoring_or_tests": ["Vital signs (standing and supine blood
   → pressure)", "Review of medication adjustments."}], "mitigation_goal": "Prevent syncope, falls, and related injuries due to sudden blood pressure drops."}, {"name": "Implement
   → fall risk mitigation strategies tailored to mobility status."}, {"name": "Patient requires walking aids and may experience transient instability after treatment
   → changes."}, {"name": "monitoring_or_tests": ["Environmental safety check", "Fall risk assessment by nursing staff."]}, {"name": "mitigation_goal": "Reduce risk of physical injury due to postural
   → instability and weakness."}, {"name": "Schedule close outpatient follow-up within 7 days post-discharge."}, {"name": "mitigation_goal": "Early reassessment is required given first-ever
   → heart failure admission, frailty, and dynamic clinical variables."}, {"name": "monitoring_or_tests": ["Clinic visit for symptoms review and lab
   → reassessment"]}], "mitigation_goal": "Ensure early detection of adverse events or clinical deterioration."}, {"name": "Optimize oxygen support as
   → tolerated."}, {"name": "Baseline hypoxemia (saturation 85%) may worsen with fluid shifts or treatment-induced changes."}, {"name": "monitoring_or_tests": ["Frequent oxygen
   → saturation checks"]}], "mitigation_goal": "Maintain adequate tissue oxygenation and avoid respiratory distress."}, {"name": "final_recommendations": "Given this patient's advanced age,
   → moderate renal impairment, mobility limitation, and low oxygen saturation, it would be prudent to intensively monitor fluid and electrolyte status, blood pressure, and
   → fall risk immediately after starting treatment. Ensuring early outpatient follow-up and carefully titrating therapies can help avert preventable complications."}
30
31The output should be formatted as a JSON instance that conforms to the JSON schema below.
32
33As an example, for the schema {"properties": {"foo": {"title": "Foo", "description": "a list of strings", "type": "array", "items": {"type": "string"}}, "required": ["foo"]}}
34the object {"foo": ["bar", "baz"]} is a well-formatted instance of the schema. The object {"properties": {"foo": ["bar", "baz"]}} is not well-formatted.
35Here is the output schema:
36```
37("properties": {"summary": {"description": "A concise, action-oriented summarization of the outcomes from different clinical analyses.", "title": "Summary", "type": "string"}, "decision": {"description": "A final decision if the patient is recommended for a home care programme or continues with stand care.", "title": "Decision", "type": "string"}, "required": ["summary", "decision"]})
38```

```

**Figure S4: CAPboard of synthetic patient 1**



## LLM-agent evaluation details

**User review (two clinicians)** Two experienced clinicians, practising specialists in emergency medicine and cardiology and not involved in the development of the tool, were recruited to evaluate user performance. Each clinician interacted with the tool across ten synthetic patient cases. The tool implemented the LLM-agents using the OpenAI GPT-4.1 model (version gpt-4.1-2025-04-14). After completing each case, the clinicians responded to a standardized set of evaluation questions focused on risk estimation, decision support, explanation quality, and clinical integration aspects. These questions are summarized in Table S6.

**Development review (one clinician)** A clinician from the development team conducted a structured internal evaluation of the tool by reviewing the same set of synthetic patients (H.S.). For each patient, two evaluation

**Table S6:** CAP component evaluation questionnaire (questions and comments). CAP=cost-aware prediction.

CAP Component	Clinical process	ID	Question/Comment
A, B (only predicted risk)	Risk estimation	Q1	The classifier's risk estimate made me more confident in assessing this patient's risk.
A, B, E	Risk estimation	Q2	The classifier's risk estimate and tool made me more confident in assessing this patient's risk.
D, E	Risk estimation	Q3	To make a risk estimate, I relied on the classifier and tool rather than my clinical judgement.
E	Risk estimation	C1	Comment about generated risk explanation.
D, F	Weighing clinical cost trade-offs	Q4	The CIP cost curves made the trade-offs between clinical costs clearer.
D, F	Weighing clinical cost trade-offs	C2	Comment about CIP cost curves: - What is beneficial about the CIP cost curves? - What is unclear or overwhelming about the CIP cost curves (e.g., cost information)?
G	Handling uncertainty	Q5	The tool suggested supportive and actionable steps to reduce uncertainty of the patient's risk.
G	Handling uncertainty	Q6	The tool made me feel falsely reassured about uncertainties I would normally question.
G	Handling uncertainty	C3	Comment about uncertainty handling.
H	Cost-aware decision guidance	Q7	The cost-aware guidance provides an informative recommendation regarding future risk.
All	Integration of patient-level and system-level reasoning	Q8	The combination of patient-level and population-level information is helpful.
All	Integration of patient-level and system-level reasoning	C4	Describe how the tool helped or hindered balancing individual vs. population-level thinking.
All	Generating explanation	Q9	The tool's explanation captured the key factors I considered when making a decision.
All	Generating explanation	Q10	I would use the explanation to communicate my decision to others (colleagues, patient, patient's family, health provider admin).
All	Generating explanation	Q11	The tool described things I already know or already had considered, superfluous information.
All	Generating explanation	Q12	The tool made suggestions outside established guidelines or evidence-based medicine.
All	Generating explanation	C5	Comment about generated explanation.

tables were completed. The first table (cf. Table S7) focused on the perceived usefulness and factual accuracy of the information generated by the tool. The second table (cf. Table S8) catalogued specific types of issues encountered, such as hallucinations, unclear language, or unrealistic suggestions. This internal review aimed to systematically document known failure modes and assess the alignment between the tool's outputs and clinical reasoning expectations.

**Table S7:** CAP component evaluation. CAP=cost-aware prediction.

CAP Component	General comments on usefulness of information	Comments on truthfulness, reliability and language	Usefulness	Accuracy
Insert value	Insert value	Insert value	Insert value	Insert value

**Table S8:** Categories of feedback issues in tool-generated suggestions.

#	Category
1	Superfluous/obvious
2	Unasked for/unsolicited
3	Repetitive
4	Incorrect terminology/use of expressions
5	Incorrect (overreaching) medical terminology
6	Hallucination (unfounded, unsubstantiated advice)
7	Overbearing, imperative advice for details, minor issues
8	Overly confident imperative advice (shall, must)
9	Unrealistic, unfeasible, idealistic advice
10	Advice to distrust/overrule classifier/reclassify
11	Unclear meaning/implication for clinician