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Forecasting disease trajectories in critical illness: comparison of probabilistic dynamic systems to static models to predict patient status in the intensive care unit

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ABSTRACT

Objective Conventional prediction models fail to integrate the constantly evolving nature of critical illness. Alternative modelling approaches to study dynamic changes in critical illness progression are needed. We compare static risk prediction models to dynamic probabilistic models in early critical illness.

Design We developed models to simulate disease trajectories of critically ill COVID-19 patients across different disease states. Eighty per cent of cases were randomly assigned to a training and 20% of the cases were used as a validation cohort. Conventional risk prediction models were developed to analyse different disease states for critically ill patients for the first 7 days of intensive care unit (ICU) stay. Daily disease state transitions were modelled using a series of multivariable, multinomial logistic regression models. A probabilistic dynamic systems modelling approach was used to predict disease trajectory over the first 7 days of an ICU admission. Forecast accuracy was assessed and simulated patient clinical trajectories were developed through our algorithm.

Setting and participants We retrospectively studied patients admitted to a Cleveland Clinic Healthcare System in Ohio, for the treatment of COVID-19 from March 2020 to December 2022.

Results 5241 patients were included in the analysis. For ICU days 2–7, the static (conventional) modelling approach, the accuracy of the models steadily decreased as a function of time, with area under the curve (AUC) for each health state below 0.8. But the dynamic forecasting approach improved its ability to predict as a function of time. AUC for the dynamic forecasting approach were all above 0.90 for ICU days 4–7 for all states.

Conclusion We demonstrated that modelling critical care outcomes as a dynamic system improved the forecasting accuracy of the disease state. Our model accurately identified different disease conditions and trajectories, with a <10% misclassification rate over the first week of critical illness.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study assesses whether modelling critical care outcomes as a probabilistic dynamic system improves forecasting accuracy of the initial trajectory of critically ill patients.
⇒ The use of dynamic feedback relationships between disease states and medications captures complex transitions among disease states, which are usually unaccounted for in conventional models.
⇒ Our model did not account for changes in the critical care population composition due to discharge and death, which may result in attrition effects resulting in discrepancies between intensive care unit days later on in the disease course.
⇒ Our model was unable to account for changes in natural history and progression of critical illness that may result in lagged effects.

INTRODUCTION

Due to the inherently dynamic nature of critical illness, the clinical trajectory of an individual patient in the intensive care unit (ICU) is often variable, modifiable and difficult to predict.[1 2] Conventional modelling strategies study associations of individual variables such as blood pressure, oxygenation and volume of fluid resuscitation at a predetermined time point, usually during the early course of the disease (admission or day 1), on outcomes of interest. While expedient, these conventional models can neither accurately capture nor integrate the constantly evolving relationship between patients' clinical status and response to therapeutic interventions. Conventional models fail to capture the complex interplay between risk factors, disease process and response to therapy, including their effect on clinical

trajectory based on predetermined time points.[3 4] At the bedside, clinical decisions in critical illness are always dynamic in nature due to the ever-changing status of critically ill patients. When researchers have tried to further understand this changing status of critically ill patients, they have, unfortunately, still almost exclusively used static time points for development of prediction models in this patient population.

Conversely, complex adaptive systems (CAS) comprise multiple, interconnected system components with inputs (eg, predictor variables observed at or as of a specific point in time), outputs (eg, predicted values of a variable at some future time point), and functions that map the inputs to an output (eg, regression models or machine learning algorithms).[1 3] System components may represent aspects of the natural history and progression of critical illness (eg, prediction models for future tidal volumes) or aspects of clinical decision-making (eg, prediction models for the likelihood of medication changes based on measures of illness severity).[5–7] By arranging components to predict future values of dynamically changing clinical variables (eg, disease severity, ventilator settings, medication administration), CAS can adapt and adjust to allow the representation of individual patient trajectories. Such dynamic approaches are needed for studies of sequential decision-making, especially within the context of multiple outcomes that coevolve over time.

Furthermore, alternative modelling approaches are urgently needed to better understand the dynamic changes during critical illness progression and the potential outcomes of therapeutic strategies under consideration. Operating rooms employ dynamic systems modelling to integrate multiple prediction models and their interrelationships to support real-time medical decision-making.[8–11] These principles, which adapt predictions of future outcomes as new data, are observed over time and can be extended to other environments (for example, ICU). By arranging components to predict future values of dynamically changing clinical variables (eg, disease severity, ventilator settings, medication administration), CAS can adapt and adjust to allow the representation of individual patient trajectories.

The COVID-19 pandemic allowed us to study a unique population with homogenous clinical mechanisms and initial trajectories of critical illness.[12 13] In this study, using a homogenous sampling of critically ill COVID-19 patients, we develop a proof-of-concept model to demonstrate how a probabilistic dynamic systems (PDS) model, comprising multiple simultaneous prediction equations for clinically relevant outcomes, can be constructed and simulated to represent critical illness disease state trajectories over time. In this pilot study, we characterised the nature of clinical trajectories in critical illness over the first 7 days of an ICU admission. In addition, we assessed the effectiveness of dynamic forecasting approaches to characterise future disease state trajectories compared with a model predicting trajectories using just the initial day's information.

METHODS

Data sources and inclusion criteria

We retrospectively studied patients enrolled in the Cleveland Clinic COVID-19 Registry from March 2020 to December 2021, which prospectively compiles clinical data obtained from the electronic medical record of all patients admitted to a Cleveland Clinic Healthcare System in Ohio, for the treatment of COVID-19. This registry is described in detail elsewhere.[13 14] Adult patients (age ≥18 years) enrolled in the Cleveland Clinic COVID-19 registry who tested positive for the SARS-CoV-2 virus via RT-PCR assay, and admitted to an ICU, were included in this analysis. Patients were excluded if on the day of ICU admission, they died or were discharged from the ICU. Included patients were classified on each ICU admission day into one of six different disease states: 1=pneumonia, 2=shock, 3=mechanical ventilation, 4=shock with mechanical ventilation, 5=resolution and 6=death. These categories were mutually exclusive and patients would fall into the highest disease state that they would meet criteria for (eg, if a patient had pneumonia with shock, they would be classified as disease state 2=shock).

Study outcomes and definitions

Four daily ICU outcomes were evaluated: (1) disease state, (2) number of vasopressors, (3) number of COVID-19 medications and (4) antibiotic use (online supplemental table 1). All variables were collected between 08:00 to 13:00 each calendar day by a team of experienced research coordinators to maintain the distinct differences in day-to-day variations for each disease state. Pneumonia was defined as presence of radiologic parenchymal infiltrates (ascertained based on reading by a board-certified radiologist). Shock was defined as the need for a continuous vasopressor infusion, and resolution was defined as an individual clinically improving and leaving the ICU physically. Vasopressor medications included norepinephrine, epinephrine, phenylephrine and vasopressin. COVID-19 medications included remdesivir, dexamethasone and other immunomodulators (tocilizumab, baricitinib and sarilumab), antibiotic use was defined as use of any intravenous or oral antibiotic for more than 24 hours. Additional baseline characteristics that were collected and accounted for in each model developed included: age, sex, body mass index and the following comorbidities: asthma, chronic cardiac disease, dialysis, COPD (Chronic Obstructive Pulmonary Disease), haematological malignancy, solid organ or bone marrow transplant, malignant neoplasm, liver disease, chronic neurological disorder and immunodeficiency or utilisation of immunosuppressive medications.

Analytic methods

We developed risk prediction models for daily changes in the four aforementioned ICU outcomes (online supplemental table 1) and applied the developed models to simulate outcome trajectories across these four outcomes over time during the first 7 days of ICU admission. To facilitate

this analysis, we randomly assigned cases to training and test cohorts using an 80%/20% ratio. We derived model estimates from the training cohort and applied these estimates to the test cohort to simulate outcomes over time and assess accuracy of simulated patient trajectories against observed values.

Risk prediction model forecasting daily disease state transitions

From the training cohort, we estimated a series of multivariable, multinomial logistic regression models to characterise the probability of being in each of the six disease states in the next day given the baseline characteristics listed above as well as the present day's disease state, number of COVID-19 medications, antibiotic use, and, for states 2 and 4, number of vasopressor medications. We estimated distinct models for each disease state (except for death) since the possible disease states into which a patient might have transitioned depended on the current day's disease state. Modelled disease state transitions are depicted in online supplemental table 1 and figure 1). As transitions from shock to mechanical ventilation (n=1 in our data), mechanical ventilation to shock (n=1) and resolution to mechanical ventilation (n=2) were very rare, we excluded these transitions from consideration in our analysis. Although transitions from resolution to death are clinically plausible, we also excluded these transitions as this did not occur during the 1-week study period.

The models predicting transitions from states 1–4 incorporated all baseline characteristics listed above. The models predicting transitions from states 2 and 4 additionally incorporated the current day's number of vasopressor medications as a covariate. The model predicting transitions from state 5 (resolution) incorporated only intercepts due to the fact that there were only 98/5839 (1.7%) patient days in which a patient transitioned from state 5 into a different state.

Risk prediction models forecasting daily medication usage

For the remaining three ICU outcomes regarding medication usage (table 1), additional forecasting models were created including the same baseline characteristics mentioned earlier. A multivariable cumulative logit model, which is a regression model for ordered categorical outcomes, that predicted the number of vasopressor medications administered (1, 2, or ≥3) when patients were in either disease state 2 (shock) or state 4 (shock with mechanical ventilation) was created. Predictions from this model were expressed as probabilities of receiving 1, 2, or ≥3 vasopressors given a patient's baseline characteristics and previous day's number of vasopressors and disease state. Similarly, cumulative logit models were created to predict the number of COVID-19 medications administered (1, 2 or ≥3) and binary antibiotic usage (yes or no) given a patient's baseline characteristics and previous day's number of COVID medications and disease state. In the model predicting the number of COVID-19 medications administered and antibiotic use, we used all patient days available in the training dataset, whereas in the model predicting the number of vasopressors administered we only used those days in which the patient was in shock.

Simulation of patient trajectories

PDS models are characterised by the simultaneous prediction of multiple variables (system components) across multiple time points. They are *probabilistic* in that predictions are represented as probability distributions over the set of possible values for each outcome. The models described above, each enable the (probabilistic) forecasting of a single outcome (disease state, number of vasopressors, number of COVID-19 medications, or antibiotic use) for the next ICU Day. Assembled as a system of probability distributions for multiple variables over multiple time points, the models enable the simulation of complex patient trajectories over time. Forecasted outcomes may be obtained at any desired time horizon, such as a series of daily forecasts that respectively take into account each day's observed outcome data to predict the next day's outcomes; or, alternatively, as a sequence of daily predictions that reflect outcome probabilities based only on information available on ICU day 1. Within an ICU day, we simulated variables in the following order: (1) disease state; (2) number of vasopressors; (3) number of COVID-19 medications; and (4) antibiotic use. Simulating the next day's disease state first was necessary in order to determine whether not simulation of vasopressors and antibiotic use for that day was applicable for that day.

Hence, we performed two series of simulations for each patient in the test cohort. The first series of simulations, which we called the *static forecasting method*, used available data on ICU day 1 only, to generate 7-day trajectories. In particular, the static models for daily transitions in disease states and medication utilisation described above were applied to simulate disease states and medication utilisation for ICU day 2 based on information available on ICU day 1; then, the simulated outcomes for ICU day 2 were applied using the same daily prediction equations to further simulate outcomes for ICU day 3; and so on; through ICU day 7. This approach is very different to the usual regression models used in predictive models in critically ill patients which takes baseline and perhaps days 1, 2 or 3 patient severity and clinical biomarker data to predict a future outcome, for example, ICU or hospital mortality or 90-day mortality. Despite the risk of changing patient trajectories impacting outcomes, this approach is still overwhelmingly used to develop models in critically ill patients. Our static model is more sophisticated that a traditional regression model, and even though our static approach actually does integrate changes in patient trajectories over time and allows those changes to propagate and impact later outcomes, it still is significantly limited in that it is based only on information available on ICU presentation. So, we developed a second series of simulations, which we called the *dynamic forecasting*

Table 1 Characteristics of 5241 critically ill COVID-19 patients admitted to Cleveland Clinic Health System by disease state on day of admission (ICU day 1)

	Pneumonia (state 1) n=3615†	Shock (state 2) n=533†	MV (state 3) n=261†	Shock with MV (state 4) n=832†
Age (years)	66 (55–75)	68 (56–78)	63 (51–73)	66 (55–75)
Sex				
Female	1552 (43%)	246 (46%)	95 (36%)	379 (46%)
Male	2063 (57%)	287 (54%)	166 (64%)	453 (54%)
Body mass index (kg/m^2)	30 (26–36)	29 (24–35)	31 (26–37)	31 (27–38)
Asthma	679 (19%)	107 (20%)	50 (19%)	164 (20%)
Chronic cardiac disease	2271 (63%)	403 (76%)	158 (61%)	587 (71%)
Chronic kidney disease	1168 (32%)	207 (39%)	71 (27%)	293 (35%)
Dialysis	420 (12%)	97 (18%)	35 (13%)	168 (20%)
Chronic obstructive pulmonary disease	1162 (32%)	184 (35%)	86 (33%)	276 (33%)
Haematological malignancy	182 (5.0%)	30 (5.6%)	13 (5.0%)	39 (4.7%)
Solid organ or bone marrow transplant	205 (5.7%)	41 (7.7%)	10 (3.8%)	55 (6.6%)
Immunosuppressive medications	1799 (50%)	267 (50%)	114 (44%)	352 (42%)
Malignant neoplasm	1291 (36%)	221 (41%)	81 (31%)	291 (35%)
Liver disease	731 (20%)	151 (28%)	60 (23%)	201 (24%)
Chronic neurological disorder	562 (16%)	144 (27%)	68 (26%)	216 (26%)
Immunodeficiency	47 (1.3%)	9 (1.7%)	2 (0.8%)	12 (1.4%)
Number of vasopressors				
0	3615 (100%)	—	261 (100%)	—
1	—	405 (76%)	—	426 (51%)
2	—	113 (21%)	—	358 (43%)
≥3	—	15 (2.8%)	—	48 (5.8%)
Vasopressor agent				
Norepinephrine	—	353 (66%)	—	693 (83%)
Epinephrine	—	90 (17%)	—	125 (15%)
Phenylephrine	—	232 (44%)	—	466 (56%)
Vasopressin	—	6 (1.1%)	—	4 (0.5%)
Number of COVID-19 medications				
0	926 (26%)	225 (42%)	85 (33%)	207 (25%)
1	914 (25%)	170 (32%)	71 (27%)	259 (31%)
≥2	1775 (49%)	138 (26%)	105 (40%)	366 (44%)
COVID-specific therapies				
Remdesivir	1946 (54%)	148 (28%)	125 (48%)	392 (47%)
Immunomodulating agents*	91 (2.5%)	5 (0.9%)	13 (5.0%)	46 (5.5%)
Dexamethasone	2494 (69%)	297 (56%)	152 (58%)	580 (70%)
Antibiotic use	2323 (64%)	451 (85%)	194 (74%)	694 (83%)

*Tocilizumab, baricitinib, sarilimumab.
†Median (IQR); n (%).
MV, mechanical ventilation.;

method. This method incorporated newly observed outcomes (as opposed to simulated outcomes) on each ICU day to predict the next day's outcomes. This method is very similar to how clinical teams make informed decisions at the bedside in this patient population. Using this method, the dynamic equations were applied to data observed on ICU day 1 to predict outcomes on ICU day 2; then, *observed* (instead of simulated) ICU day 2 outcomes were applied to predict outcomes on ICU day 3; and so on; up to ICU day 7. The intent of developing both static

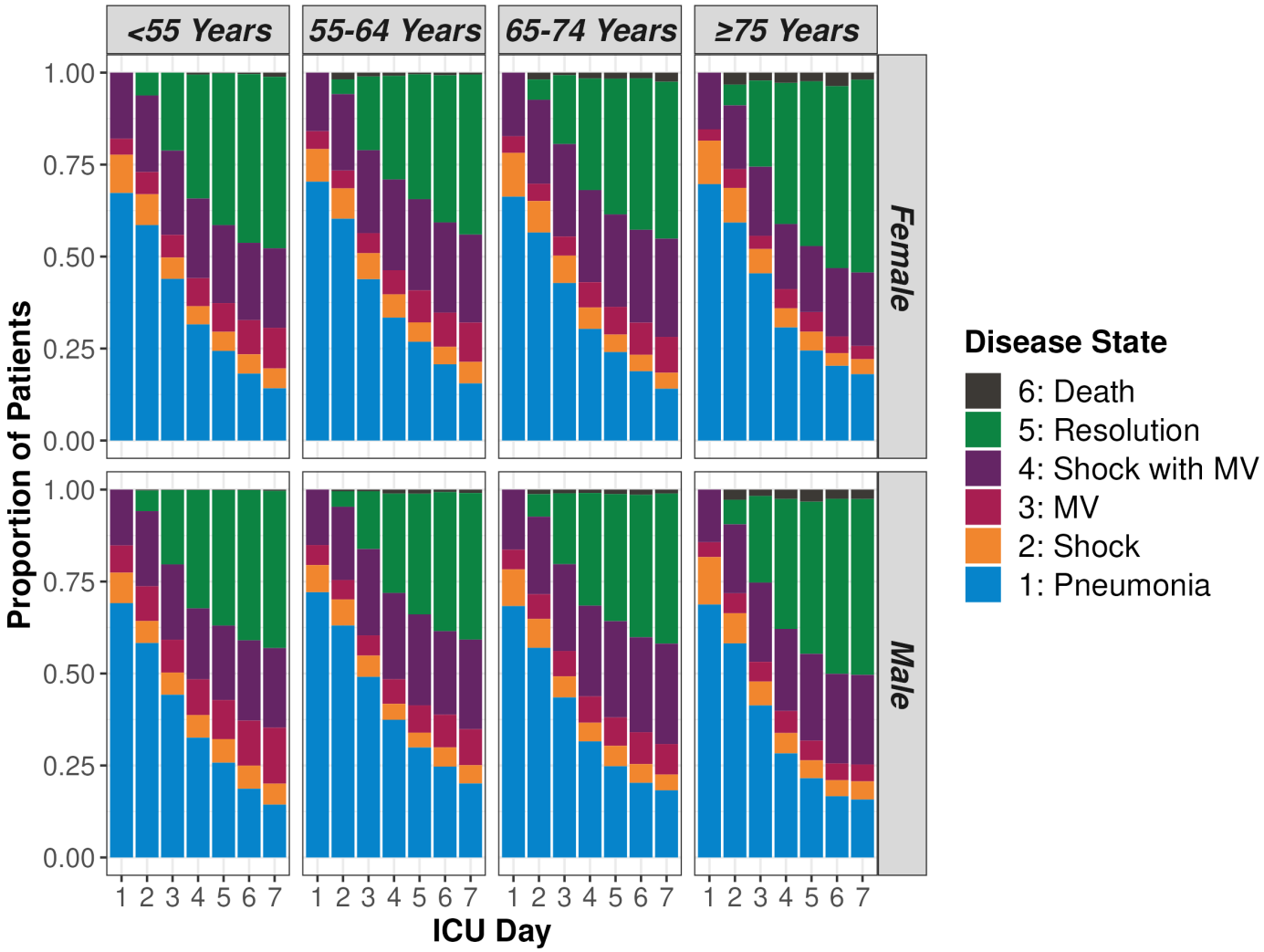

Figure 1 Distribution of illness states by age category, sex and ICU day (1–7). MV, mechanical ventilation.

and dynamic models was not to compare them from a statistical standpoint, but rather, to show the clinical implications of the two modelling approaches. Both these modelling approaches account for interdependence and the dynamic nature of critically ill patients much better than a conventional regression model.

We simulated 1000 trajectories for each patient in the test cohort using each of these two forecasting methods (static and dynamic modelling). We then derived, from the simulation output, forecasted probabilities for each outcome variable on each of ICU days 2–7 for each patient. These probabilities were computed as the proportion of simulation 'runs' in which a given outcome was equal to a given value (eg, 128/1000 simulations in which a patient was on mechanical ventilation on ICU day 3 represented a 0.128 forecasted probability). Forecasted outcome probabilities were assessed for accuracy against observed outcomes, and R statistical software V.4.0.3 (R Core Team, 2020) was used for all analysis. See the Supplement, under 'online supplemental methods', for details.

Patient and public involvement

None.

RESULTS

Baseline characteristics

Of 5492 patients whose data were available in the Cleveland Clinic COVID-19 ICU registry, 76 died on the day of presentation to the ICU and 46 patients were discharged on ICU day 1, and were excluded. We also removed 129 patients due to the unavailability of complete data. This resulted in a total analysed sample size of 5241 patients. Of these, 3615 (69.0%) were in pneumonia (without shock or mechanical ventilation), 533 (10.2%) were in shock, 261 (5.0%) were mechanically ventilated and 832 (15.9%) were in both shock and were mechanically ventilated on ICU day 1. There were 4054 patients (77.4%) who remained in the ICU through the entire 7-day study period; 147 (2.8%) were discharged from the ICU on ICU day 2, 158 (3.0%) on day 3, 230 (4.4%) on day 4, 281 (5.4%) on day 5 and 371 (7.1%) on day 6. The analysed sample contained 28 439 records of consecutive ICU days observed within a patient (eg, data for both ICU days 3 and 4). The training dataset included 22 728 records of consecutive ICU days among 4193 patients, and the test dataset included 5711 records

of consecutive ICU days among 1048 patients (online supplemental table 2).

Summary statistics for demographic and clinical characteristics on ICU day 1 are presented by initial disease state in table 1. Patients who were in shock with or without mechanical ventilation (states 4 and 2, respectively) on ICU day 1 were associated with somewhat higher comorbidity burden than patients who were in the other two initial disease states (pneumonia without shock or mechanical ventilation, and mechanical ventilation without shock), including higher prevalence of cardiac disease, kidney disease, dialysis requirement and liver disease. These patients were also more likely to have received antibiotics. Patients who had pneumonia without shock or mechanical ventilation (state 1) on ICU day 1 were more likely to receive remdesivir. Patients in states 1 (pneumonia without shock or mechanical ventilation) and 4 (shock with mechanical ventilation) on ICU day 1 were more likely to receive dexamethasone.

Distributions of disease states within each ICU day are presented in figure 1 by age category and sex. Generally, these distributions were stable across groups. Percentages of patients in shock (state 2), mechanical ventilation (state 3) and shock with mechanical ventilation (state 4) were largely consistent across ICU days, while the per cent of patients who were in pneumonia without shock or mechanical ventilation (state 1) gradually declined and the per cent of patients in resolution (state 5) gradually increased.

Simulation of patient trajectory based on disease state

Table 2 includes measures of classification and probabilistic prediction performance for dynamic (next day) predictions of disease state, which were derived from the test cohort. When the next day's disease state was predicted to be pneumonia (ie, state 1 had highest predicted probability among the 1000 simulations for a specific patient day), the misclassification rate in the test dataset was 559/5711 (9.8%) and the overall AUC (95% CI) for state 1 predicted probabilities was 0.937 (0.931 to 0.944). For state 2, the misclassification rate was 218/5711 (3.8%) and the AUC was 0.909 (0.887 to 0.931). Similarly, these statistics were 203/5711 (3.6%) and 0.953 (0.942 to 0.965) for state 3 (respectively); 325/5711 (5.7%) and 0.945 (0.937 to 0.953) for state 4; 561/5711 (9.8%) and 0.918 (0.909 to 0.927) for state 5; and 68/5711 (1.2%) and 0.755 (0.695 to 0.815) for state 6. Calibration performance of these predicted probabilities was excellent for each of the six states (see figure 2).

AUC estimates for predicted probabilities of being in each disease state as a function of ICU day, comparing static (using data from only ICU day 1 to forecast outcomes through ICU day 7) versus dynamic (using each day's observed data to forecast the next day's outcomes) forecasting approaches, are depicted in figure 3. AUCs were equal between static and dynamic approaches for ICU day 2 since the predictions were based on the same exact information (data from ICU day

Table 2 Prediction performance of daily disease state transitions within the test cohort

Illness state	Classification performance (state with highest predicted probability)							Probabilistic prediction performance		
	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV	Accuracy	F1 Score	AUC (95% CI)
1: Pneumonia	1997	559	3155	0	1.00	0.85	0.78	1.00	0.90	0.88	0.937 (0.932 to 0.943)
2: Shock	229	132	5264	86	0.72	0.97	0.63	0.98	0.96	0.68	0.909 (0.885 to 0.934)
3: MV	300	95	5208	108	0.73	0.98	0.76	0.98	0.96	0.75	0.953 (0.942 to 0.965)
4: Shock with MV	1029	138	4357	187	0.84	0.97	0.88	0.96	0.94	0.86	0.945 (0.937 to 0.953)
5: Resolution	1189	43	3961	518	0.70	0.99	0.96	0.88	0.90	0.81	0.918 (0.910 to 0.926)
6: Death*	0	0	5643	68	0.00	1.00	—	0.99	0.99	0.00	0.755 (0.695 to 0.816)

Performance was assessed based on both classification (disease state for which the model assigned the highest predicted probability) and probabilistic predictions.
*There were no circumstances where death was the state with the highest predicted probability.
AUC, area under the receiver-operating characteristic curve; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

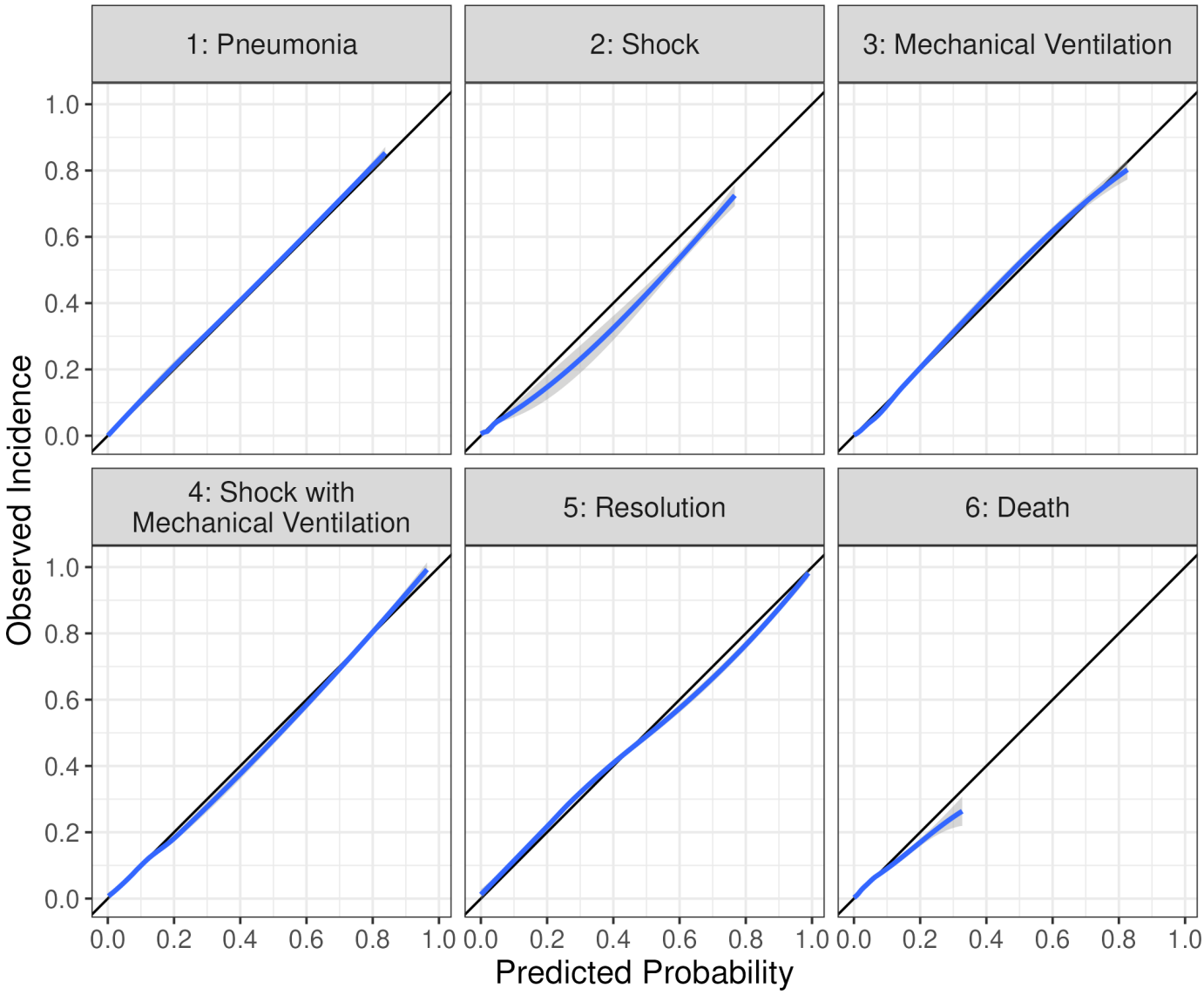

Figure 2 Calibration performance for next day predicted probabilities of being in each of the six modelled illness (or death) states. Perfect calibration is indicated when the estimated calibration curve aligns with the 45° line through the origin.

1). For ICU days 2–7, the dynamic forecasting approach was stable or even increasing in AUC as a function of time. AUC values for the dynamic forecasting approach were all above 0.90 for ICU days 4–7 for all states except for death, for which there were only 68 observed events in the test dataset. In contrast, the accuracy of the static approach steadily decreased as a function of time, with AUC values for each health state below 0.8 for ICU days 4–7. Simulation of patient trajectory was based on medication utilisation.

The AUC for next-day predictions of antibiotic use was 0.944 (0.936 to 0.951). The RMSE (95% CI) for next-day predicted number of COVID-19 medications administered was 0.395 (0.388 to 0.402) (online supplemental figure 2). The RMSE for next-day predicted number of vasopressors administered during shock with (state 4) or without (state 2) mechanical ventilation was 0.388 (0.375 to 0.402) (online supplemental figure 3).

DISCUSSION

We demonstrated that modelling critical care outcomes as a PDS improves forecasting accuracy of the disease state over the first 7 days of an ICU admission. We report that, in patients with COVID-19 associated critical illness, a PDS model accurately identified disease trajectories, with a relatively low misclassification rates (<10 %). These predictions improved or remained appropriately stable with the dynamic forecasting approach that adapted predictions daily based on newly available information, unlike static approaches that rely only on information available early in the ICU stay and become less accurate over time. These results indicate that future models created to predict patient trajectories should incorporate a dynamic approach, evaluating real-time patient parameters, rather than modelling with the traditional static variables collected at baseline or at fixed periods over multiple days.

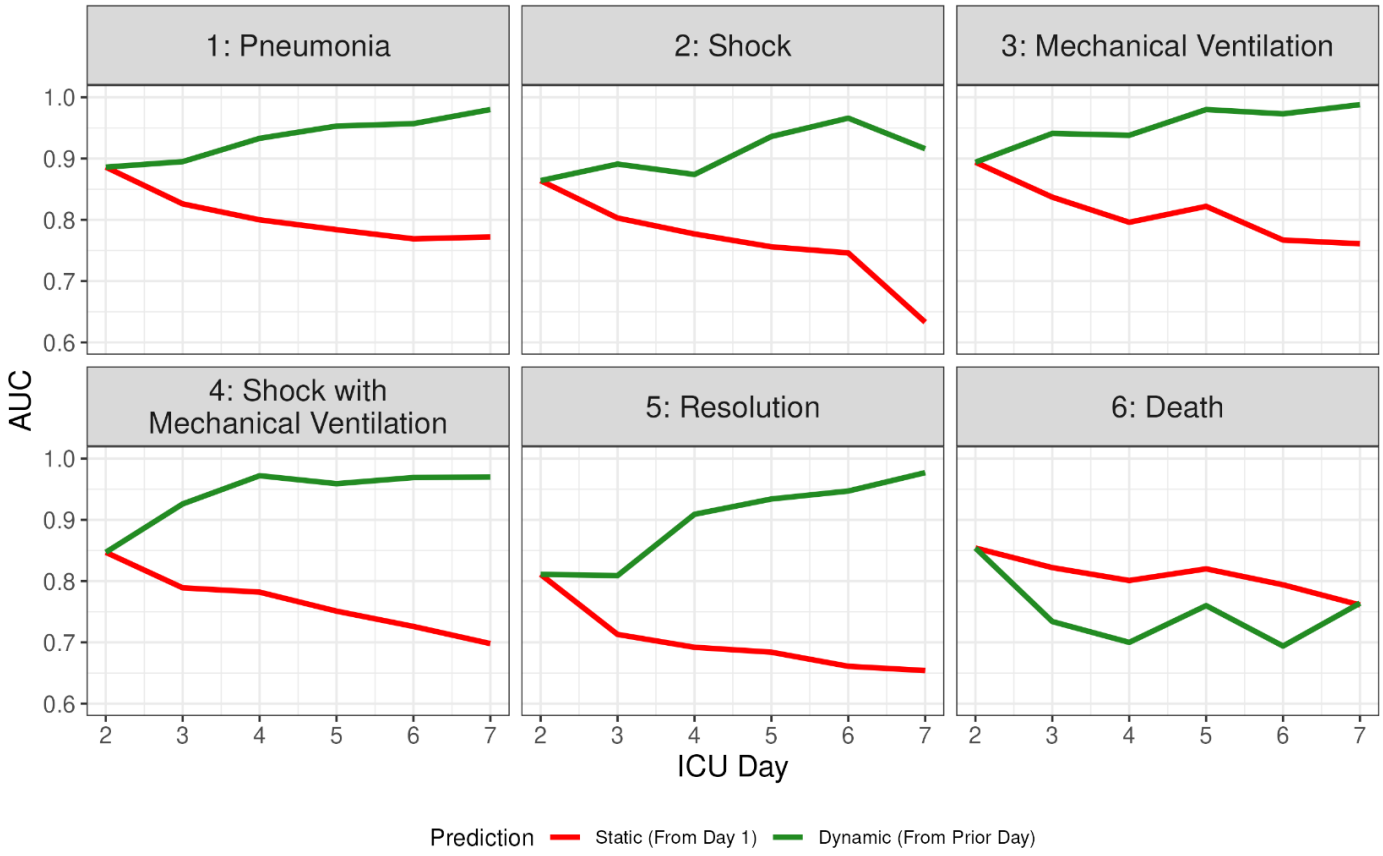

Figure 3 Area under the receiver operating characteristic curve as a function of intensive care unit (ICU) day, comparing static versus dynamic forecasting approaches. The static approach relied only on data observed in ICU day 1, while the dynamic forecasting approach incorporated each day's observed data in predicting the next day's outcomes.

We also demonstrated that PDS modelling allows for a clinically meaningful overview of disease state transition, capturing both the uncertainty and instability associated with critical care illness. Conventional prediction models that use either clinical variables or severity of illness scores at the time of admission have been used as prediction tools for mortality or clinical decisions. But these models conceptually cannot identify and align with the changing disease trajectories in critically ill patients.[15–17] Consequently, such models underperform when applied over the disease course and, as a result, lose their discrimination power over time.[16 17] Although recent studies have used static models to account for changing risk factors by recomputing risk factors over time, they are still static equations that do not account for interrelationships between disease states, therapies and outcomes.[18] As shown in our study, the use of static models improves the understanding of disease trajectories, but our PDS model consistently outperformed static approaches to prediction of disease states and as such could be used to produce actionable information related to complex transitions in critically ill patients (ie, development of shock) or addition of clinical resources (ie, need for mechanical ventilation).

Moreover, complex forecasting systems like PDS models are grounded in the concept that trajectories of critical care management and outcomes over time are the product of multiple, coevolving relationships.[1 4] We consider this as a changing 'paradigm' and also as an opportunity for advancing the understanding and effectiveness of models in critical care. Further research into this modelling technique will help improve forecasting accuracy while helping us understand the potential impacts and tradeoffs among different clinical management strategies. The approach we have employed involves a combination of knowledge representation (ie, the specification of a systems structure including relationships among variables over time by experts in critical care) and empirical estimation. It is our contention that manual specification of dynamic systems by clinical researchers is essential for the ultimate translation of these models to the bedside. Alternative machine learning approaches that are being employed in clinical research attempt to learn the structure of a system via algorithms and are not guaranteed to produce clinically relevant relationships. This current approach is a necessary step to develop a system-based approach to clinical scenarios that are meaningful to bedside clinicians.

We compared a static approach that simulated 7-day trajectories using only data from ICU day 1 to a 1-day-ahead dynamic forecasting approach that applied newly observed outcomes for each ICU day to predict the next

day's outcomes.[19] Similar to weather forecasting, where new information is routinely applied to update forecasts, dynamic ICU forecasting models predict trajectories over a fixed number of days ('k-step ahead' forecasts) in line with the collection of new data over time.[20] We employed a simulation-based approach to achieve these forecasts, allowing predictive relationships to interact (or coevolve) over time.[21] In concept, static risk models can be reapplied to new outcome data which accrues over time in the ICU (eg, recomputing the SOFA (Sequential Organ Failure Assessment) and SAPS (Simplified Acute Physiology) scores each day); however, this does not constitute an adaptive system in which outcomes of the whole are greater than the sum of its parts.[22 23]

Recent studies in critical care have focused on multistate survival modelling to assess complex, dynamic changing systems.[5 12 24] These models are capable of capturing transitions among disease states, such as those we have modelled. Such multistate models would be very useful in studying outcomes compared with a conventional regression model. However, they are focused on a single outcome and do not accommodate dynamic feedback relationships between disease state and medication use that our analysis has highlighted. Hence, these data presented are important initial steps towards accurate prediction and forecasting of disease trajectories in critical illness.

A limitation to our analysis is that it assumes a *Markovian* system, that is, that the nature of dynamic relationships (disease state transitions or changes in medications) is stable and consistent over time: that is, the relationships are the same for day t to day (t+1) regardless of the value of t.[19 25] Changes in the structure of the critical care population due to discharge and death may result in *residual cohort* or *attrition* effects which can influence these relationships such that they may be different for specific ICU days as opposed to being uniformly described across ICU days. Likewise, changes in natural history, progression of critical illness may involve lagged effects (such as delayed effects of inflammatory processes or treatments administered) such that these effects may be less applicable for certain ICU days than for other ICU days. Additionally, introduction of new therapeutic intervention (eg, development and dissemination of COVID-19 vaccinations) may impact model prediction performance if the changes occurred during the time frame of the study.

The objective of this proof-of-concept analysis was to use prospectively collected data from a relatively homogeneous population of COVID-19 patients admitted to the ICU to demonstrate the applicability and potential value of PDS modelling. Translation of the model to the COVID-19 care setting was not necessarily the goal. Declining numbers, improvement in both population immunity and medical management make prediction of COVID-19 progression perhaps, superfluous. This is a first but deliberate step towards refining and applying PDS modelling principles to other disease processes, eventually with a goal to optimise treatment strategies for any given patient. The focus is to explore the ongoing interplay between treatment strategies, response to treatment and disease state transition. To ensure the external validity of the resultant dynamic models, careful selection of predictor variables needs to be undertaken. This model used factors important for critically ill patients; however, different practice areas and patient populations will require individualisation of the factors selected for inclusion in the specific model for development. Finally, like any prediction model, internal, external and prospective validation will be needed to assess the clinical and research utilisation of these modelling strategies.

In conclusion, developing clinically relevant dynamic forecasting models represents a major undertaking and is the future of prediction and decision-making research in critical care. These models have the potential to transform both our understanding and the practice of critical care while providing individualised patient care.

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Data availability statement Data are available upon reasonable request. All the data used in the study has been presented as figures and tables. For requests related to the raw data related to any further analysis, please reach out to the corresponding author. Data would be provided after appropriate data user agreements are in place.

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