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Computational Tools for Personalizing Treatment of Acute Respiratory Failure, from Machine Learning to Digital Twins: A Narrative Review

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Abstract

Patient-specific computational tools hold great promise for the development of more personalized treatment strategies for acute respiratory failure. Such tools span a continuum from data-driven predictors, to patient-specific mechanistic models, and ultimately to fully realized digital twins with continuous bidirectional model-patient interactions. Data-driven prediction models apply machine learning to large-scale patient datasets to develop tools that can help clinicians identify patients who are likely, or unlikely, to benefit from a particular course of treatment. By incorporating detailed computational representations of disease pathophysiology, patient-specific mechanistic models can provide insights into the effects of existing or novel treatment strategies, support patient stratification and treatment personalization, and enable the design of *in silico* clinical trials of new interventions. Finally, fully realized dynamic digital twins of patients could provide real-time decision support and ‘simulate-before-treat’ capabilities at the bedside, helping clinicians optimize treatment as the patient’s disease state evolves.

This narrative review provides an overview of recent research applying these approaches in the context of acute respiratory failure, encompassing both respiratory and ventilatory support across neonatal, paediatric and adult populations, and pre-hospital, ward and intensive care environments.

Introduction

Respiratory support and mechanical ventilation remain the mainstays of treatment delivered by critical care clinicians for acute respiratory failure (ARF) in neonates, children and adults. Non-invasive support modalities such as high-flow nasal cannula (HFNC) therapy [1], continuous positive airway pressure (CPAP) [2], or non-invasive ventilation (NIV) [3] can improve gas-exchange, reduce patients' spontaneous respiratory efforts, and improve outcomes, while avoiding the risks associated with tracheal intubation. In the severest cases of respiratory failure invasive mechanical ventilation (IMV) in the intensive care unit (ICU) is life-saving and is also mandatory during many surgical procedures [4].

However, despite extensive research, limited progress has been made in personalising treatment, with the current standard of care for IMV still being largely based on protocols derived from the 2000 ARDSnet randomized controlled trial (RCT) [5]. Researchers in this area of medicine face many unique challenges, including the physiological complexity of the respiratory system; patient heterogeneity; highly dynamic disease trajectories; the ethical, practical and cost implications associated with experimental research in large animal models; the comparatively small numbers of critically ill patients available for enrolment in RCTs; the difficulties in accurately measuring many important physiological parameters *in vivo*, particularly in spontaneously breathing patients; continuing uncertainty regarding the precise mechanisms underlying potentially injurious iatrogenic patient-ventilator interactions; and the complexity and variety of modern forms of non-invasive and invasive respiratory support.

Patient-specific computational tools have the potential to address many of the above challenges. It is important to distinguish such tools from more general computational models, which have a long history of useful contributions in mechanical ventilation [6]. The key distinguishing feature is their ability, only recently realized, to *credibly replicate the responses of individual patients to* *a specific treatment* with sufficient fidelity to support prediction. This capability underpins their huge potential for advancing medical research and patient care [7–10].

Such tools span a continuum, from data-driven predictors, to patient-specific mechanistic models, and ultimately to fully realized digital twins with continuous bidirectional model-patient interactions (Figure 1). Data-driven prediction models apply machine learning and other AI methodologies to large-scale patient datasets to create models that can identify subtle patterns in patient data and help predict important patient outcomes that are difficult or impossible to model ‘mechanistically’ (e.g., hospital length-of-stay, mortality, extubation, etc.). In the context of ARF, such tools have shown particular promise to help manage transitions between non-invasive and invasive forms of respiratory support [11]. Patient-specific mechanistic models are based on computational representations of biological and physiological processes, grounded in established physical, chemical, and biological laws. They explicitly represent the pathophysiology of the underlying disease, and when matched to individual patient data can provide insights into the effects of different ventilation strategies, facilitate stratification of patients and personalisation of treatments, and create the possibility of implementing faster, cheaper, and more targeted *in silico* clinical trials [12]. This potential is particularly relevant in the context of ARF, where research into ventilation strategies has made limited progress in terms of personalization [13], large-animal models are required for experimental research, and RCTs are extremely costly and slow to recruit, with such low success rates (typically < 40%) [14] that some clinicians have even called for their use to be abandoned [15]. Finally, fully realized dynamic digital twins of patients use bi-directional information flows to continuously track changes in a patient’s disease state, providing real-time decision support and ‘simulate-before-treat’ capabilities at the bedside [16]. Although, such digital twins are now poised to revolutionize healthcare [17] – a PubMed search for 'digital twins' retrieves over 1,700 citations since 2020, with an exponential increase year-on-year [18] – their implementation in the context of ARF remains to be fully realized.

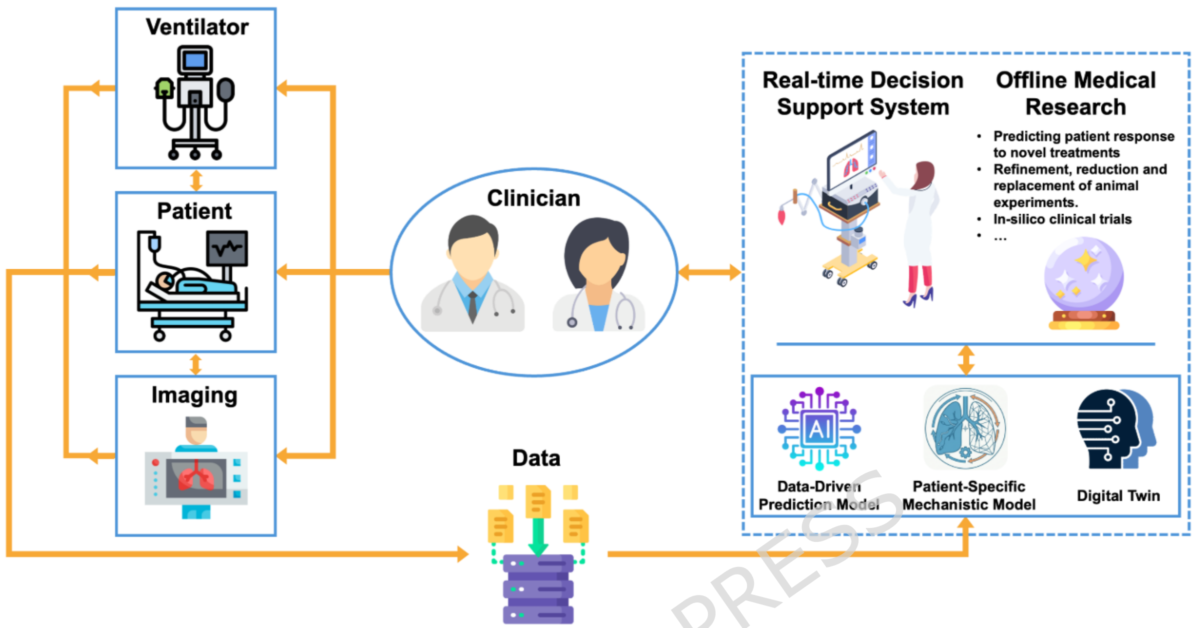

Figure 1: Potential of patient-specific computational tools in the treatment of ARF

In this review, we aim to provide a narrative overview of recent research in developing and applying patient-specific computational tools to advance research into the treatment of ARF, encompassing both invasive and non-invasive respiratory support; neonatal, paediatric and adult patients, and pre-hospital, ward and intensive care environments. We conducted a PubMed search (inception until April 16th, 2026) for English-language literature related to the treatment of ARF containing the terms mechanical ventilation, non-invasive ventilation, digital twin, computational model, mathematical model, machine learning, or artificial intelligence, and screened titles and abstracts to identify studies that included patient-specific computational tools as described above.

Non-Invasive Respiratory and Ventilatory Support

Background and Clinical Challenges:

Non-invasive respiratory and ventilatory support, including high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and non-invasive ventilation (NIV), is widely used in the management of both acute and chronic respiratory failure [19], but presents several important clinical challenges. Many important patient parameters are not measurable in routine clinical practice in spontaneously breathing patients, interactions between the patient's respiratory effort and the external support are often difficult to assess. As a result, personalization of support remains challenging, and significant uncertainty exists regarding the criteria for treatment escalation.

Patient-Specific Mechanistic Models to Personalize HFNC Therapy:

HFNC therapy delivers heated, humidified gas at flow rates generally exceeding patient inspiratory demand, resulting in multiple beneficial physiological effects, including washout of anatomical dead space, generation of positive end-expiratory pressure (PEEP), modulation of inspiratory effort, improvement in oxygenation, and improved carbon dioxide (CO_2) elimination. However, the magnitude and relative contribution of these effects vary substantially across individuals, depending on lung mechanics, respiratory drive, airway resistance, upper-airway geometry, and disease phenotype [20]. This marked inter-patient variability has motivated the development of patient-specific mechanistic models to investigate HFNC mechanisms and guide personalisation of treatment. In contrast to population-averaged physiological studies, patient-specific mechanistic models aim to replicate the behaviour of an individual patient by calibrating a computational cardiopulmonary model to patient-specific measurements. HFNC is particularly amenable to this approach because its physiological effects are subtle, strongly flow-dependent, and highly modulated by a patient's spontaneous respiratory effort and pattern of breathing, making treatment optimisation at the bedside challenging.

Since their introduction, computational models have been used to investigate the physical and physiological mechanisms underlying HFNC therapy. In particular, computational fluid dynamics (CFD) models were employed to characterize airflow patterns, pressure distribution, and dead-space washout in anatomically realistic upper-airway geometries [21,22]. These studies demonstrated how cannula geometry, flow rate, and nasal anatomy can influence treatment effects. While such simulations were not calibrated to individual patient data, they provided foundational mechanistic insights into HFNC flow dynamics and pressure generation, establishing modelling frameworks and boundary conditions that underpin recent work using digital twins of patients receiving HFNC therapy.

Shamohammadi *et al.* employed a mechanistic cardiopulmonary simulator to model physiological data on arterial blood gases, tidal volume and oesophageal pressure swings (ΔP_{es}) from 58 adult patients with acute hypoxemic respiratory failure (AHRF) receiving HFNC therapy with a flow rate of 60 L/min [23]. Simulations using the patient-specific models suggested that HFNC can generate substantially higher mean airway pressures in diseased lungs than was previously inferred from studies in healthy volunteers. These findings suggest that patient-specific lung mechanics and reduced functional lung volumes in AHRF could significantly influence HFNC-generated airway pressures, with important implications for both alveolar recruitment and the risk of overdistension.

In a separate 2025 study, the same group developed personalized models of 10 adult AHRF patients receiving HFNC using individual measurements of arterial blood gases, ΔP_{es} , and tidal volume at variable HFNC flow rates [24]. Patient data were obtained from cohorts monitored with electrical impedance tomography (EIT) and oesophageal manometry at baseline and at increasing flow rate settings. The resulting models accurately reproduced measured patient responses at multiple flow rates, enabling the investigation of the physiological effects of HFNC flow escalation. Simulations revealed the existence of two distinct patient groups. In 'responders' increased HFNC flow rates reduced inspiratory effort and improved dynamic compliance, whereas in 'non-responders' higher flow rates increased respiratory effort and multiple indices associated with potential patient self-inflicted lung injury (P-SILI). This study provided additional mechanistic evidence that the effects of HFNC therapy are inherently patient-specific, further motivating efforts to personalize treatment when using this form of respiratory support.

Most recently, this group used the same approach to explore bi-level HFNC, a novel strategy (previously only tested in healthy subjects [25]) in which inspiratory flow rate is set to be higher than expiratory flow rate [26]. Patient-specific models were constructed for 13 patients with AHRF and 17 patients with sepsis using detailed physiological measurements, including arterial blood gases, tidal volume, and oesophageal pressure swings at multiple HFNC flow settings. Simulations with bi-flow HFNC compared with conventional HFNC predicted substantial reductions in inspiratory effort, improvements in dynamic compliance, and reductions in indices associated with lung injury. These results were preserved across both AHRF and sepsis subgroups and illustrate the potential of patient-specific models to evaluate potential benefits of novel treatment strategies in different patient groups prior to clinical testing.

Patient-Specific Mechanistic Models to Personalize NIV:

Patient-specific mechanistic models were also developed by Weaver *et al*. to investigate mechanisms underlying the success or failure of NIV [27]. This study used patient data from a pilot-study in 30 patients with moderate-to-severe *de novo* AHRF patients who had failed HFNC therapy and subsequently underwent a trial of NIV [28]. The pilot study found that a reduction of more than 10 cmH_2O in ΔP_{es} after two hours was the only statistically significant indicator of NIV success at 24 hours in this patient cohort, but was unable to fully elucidate the underlying mechanistic basis for this result. By creating and analysing mechanistic models of each patient from the initial study, Weaver *et al*. subsequently demonstrated that the ΔP_{es} reduction reported was associated with a corresponding improvement in respiratory mechanics and a reduction in P-SILI indices to levels below the thresholds deemed injurious in IMV, providing a mechanistic explanation for the observed variation in treatment response in different patients.

Data-Driven Prediction Models in Non-Invasive Respiratory Support:

When successful, non-invasive respiratory support removes the need for, or reduces the length of, ICU stay, avoids risks associated with intubation, and lowers risk of death [29,30]. However, a growing body of evidence also suggests that patients who ultimately fail non-invasive support and subsequently require IMV have a higher risk of mortality, potentially due to clinicians persisting too long with a failing strategy [3,30,31]. Identifying these patients early in their course of treatment is one of the key open problems in the clinical management of AHRF, as no formal guidelines are currently available to assist in determining whether an individual patient is at risk of failing non-invasive support [32]. Once support is initiated, various threshold values based on clinical scores or indices have been proposed to help identify patients who are at higher risk of failure and need treatment escalation [33], but significant uncertainty exists regarding their optimal timing and cut-off values. Additionally, validation of their predictive accuracy on external datasets is rare, and their effectiveness in prompting escalation of treatment is low [34].

A promising approach to address this problem is to develop data-driven machine learning models that can assist in identifying patients who may require closer monitoring or treatment adjustment/escalation. Compared with conventional clinical scores or indices, which are typically based on static, single-time-point measurements, machine learning models can deal with more complex, multiple time-point datasets and detect subtle patterns that capture temporal trends associated with clinical deterioration.

Several different machine learning models have been used to predict the outcome of either HFNC or NIV – see Table 1. However, most of these studies [35–44] use data from unspecified time points within 6-, 8- or 24-hour windows and/or lack rigorous validation on multi-centre external datasets (a recent review on the use of machine learning models in the context of intensive care medicine noted that only 5% of 172 articles examined had validated their results on external data, i.e. on data from a source other than the one used for model training [45]).

Cheng *et al.* developed an ensemble machine learning model using measurements from two timepoints prior to, and at the initiation of, HFNC [46]. Although external validation was performed, the relatively small internal validation cohort and the use of a single-centre external validation cohort resulted in a large performance gap between internal and external validation results. Yu *et al.* developed a support vector machine (SVM) machine learning model for HFNC outcome prediction using only measurements obtained within the first two hours of treatment [47]. Using a rigorous, nested, cross-validation framework and external validation across multicentre datasets, the resulting data-driven model was shown to consistently outperform standard clinical indices in predicting HFNC outcomes.

Large language models (LLMs) have also demonstrated impressive capabilities. Liu *et al.* conducted a study evaluating the accuracy of ChatGPT in predicting HFNC outcome after 6 hours of treatment [43]. Rather than using structured numerical inputs, they used prompts based on natural language questionnaires that described each patient's clinical history and physiological status. In prospective testing GPT-4.0 achieved an area under the curve (AUC) of 0.82, demonstrating predictive performance comparable to that of specialist respiratory physicians (AUC 0.782), and markedly superior to non-specialist physicians (AUC 0.662).

In contrast to traditional machine learning models that require extensive retraining on each new task, LLMs or foundation models can perform downstream tasks without additional training by leveraging in-context learning [48]. This approach could be particularly valuable in clinical settings, where access to large, labelled medical datasets is limited and patient privacy concerns

Table 1 Overview of data-driven models for predicting outcomes of non-invasive respiratory support (NIRS). AUCs given for external datasets when available.

Study Reference	Year	Prediction Target	Prediction Time Window	Machine Learning Model(s)	Key Predictive Features	Primary Performance (AUC)	Validation Datasets
Models developed for NIRS, including HFNC, CPAP, and NIV							
Bendavid *et al*. [35]	2022	COVID-19 patients	6-24 h windows after NIRS initiation	XGBoost with Transfer Learning	RR, pH, HR, $PaCO_2$	0.80	Internal + External
Essay *et al*. [41]	2023	Patients with mild or moderate hypoxemia	1-72 h windows after NIRS initiation	LSTM	RR, HR, SpO_2	0.96	Internal
Fu *et al*. [38]	2024	Patients with mild or moderate hypoxemia	6 h preceding and 24 h within the ICU admission	AdaBoost	SOFA, APSIII, lactate, GCS	0.73	Internal
Models developed for HFNC only							
Hendriks [40]	2023	Patients receiving HFNC	Within 8 h after HFNC start	Random Forest	ΔFiO_2, mean FiO_2, mean SpO_2, LDH	0.73	Internal (nested CV)
Wang *et al*. [39]	2024	Patients with ARF	Not specified	Random Forest	LODS, GCS, oxygenation index, lactate	0.83	Internal
Yang *et al*. [42]	2024	COVID-19 patients	First 24 hours of ICU admission	XGBoost	PaO2, arterial pH, Age	0.76	Internal
Liu *et al*. [43]	2024	Patients receiving HFNC	Two timepoints: at HFNC initiation and 6h thereafter	ChatGPT	GCS, SpO_2, pH, PaO_2, $PaCO_2$	0.82	Prospective
Cheng *et al*. [46]	2025	Patients diagnosed with AHRF	Two timepoints: at ICU admission and at the start of HFNC	Ensemble Learning	GCS, SOFA, albumin, ROX index, sepsis	0.75	Internal + External
Yu *et al*. [49]	2025	AHRF patients	Two timepoints: at HFNC initiation and 2 h after	SVM	RR 2h after, HR 2h after, ΔFiO_2, ΔRR, HR 2h after	0.79	Internal (nested CV) + External (multicentre)

Models developed for NIV only							
Feng *et al.* [36]	2021	Patients undergoing NIV.	8-48 h windows after NIV start	TULightGBM (LightGBM + Attention)	Age, MBP, SBP, SpO_2	0.83	Internal
Wang *et al.* [37]	2022	Patients received NIV following extubation	Within 6 h of NIV start	CatBoost	MV duration, respiratory rate, GCS	0.87	Internal + Prospective
Liang *et al.* [44]	2022	Patients primarily diagnosed with AECOPD, pneumonia, or ARDS	Two timepoints: before NIV initiation and 1-2 h after NIV initiation	Stacking ensemble algorithm	Oxygenation index, pH and FiO_2 collected 1 h after NIV	0.91	Internal
Yu *et al.* [50]	2025	AHRF patients	Two timepoints: before NIV initiation and 1-2 h after	TabPFN	P/F and RR 1-2h after, Δ pH, P/F, Δ FiO_2	0.76	Internal (nested CV) + External (multicentre)
Yu *et al.* [11]	2026	Patients with AHRF and patients with acute-on-chronic hypercapnic respiratory failure	Two timepoints: before NIV initiation and 1-2 h after	*NIVPredict* (TabPFN)	P/F and RR 1-2h after, Δ pH, P/F, Δ FiO_2, SAPSII	0.85	In-hospital testing

can restrict data sharing. Recently, a foundation model specifically developed for small-to-medium-sized tabular data processing was proposed, which was pretrained on large synthetic distributions of tabular tasks [51]. This model may be particularly suited to critical care applications, where obtaining large, correctly labelled datasets for every specific scenario or patient subgroup is often infeasible. Recent multi-centre validation studies using this model in the context of non-invasive respiratory support demonstrate its ability to predict HFNC and NIV outcome with superior accuracy to established clinical scores and indices [49,50]. A web-based decision support tool, *NIVPredict*, [11], has recently been developed which extends the model developed in [49,50] to patients with ARF from more heterogeneous aetiologies. In-hospital evaluation of the tool by clinicians demonstrated promising real-world performance, supporting its potential clinical applicability.

Future development of these tools could exploit synthetic data generated by digital twins that can estimate physiological variables that are difficult or impossible to measure directly, to deliver enhanced predictive performance and interpretability.

Invasive Mechanical Ventilation

Background and Clinical Challenges:

The use of computational modelling in the context of IMV has a long history [52]. As with non-invasive respiratory support, many physiologically important parameters and indices associated with ventilator-induced lung injury (VILI) are difficult or impossible to measure directly in routine clinical practice. Clinicians must also make complex decisions regarding ventilator settings, recruitment strategies, and the timing of weaning and extubation, often in the presence of considerable physiological uncertainty. Recent research in this area using computational tools has focused on their use in investigating VILI [53], in evaluating novel modes of mechanical ventilation, and in clinical decision support, as well as in the development of novel closed-loop ventilation systems.

Patient-Specific Mechanistic Models to Investigate VILI:

Several studies using patient-specific mechanistic models have investigated methods for titrating PEEP to minimize the risk of VILI. Chiew *et al.* used mechanistic models of 10 patients with acute respiratory distress syndrome (ARDS) to develop an at-the-bedside method for titrating PEEP to optimize lung elastance [54], while Chikhani *et al.* used 12 mechanistic models of ARDS patients to demonstrate the potential for high PEEP to lead to decreased oxygen delivery to tissues [55]. Patient-specific mechanistic models have also been developed that can predict mechanical responses to altered PEEP [56], and a desktop application named CURE Soft has been developed, which can be used for real-time optimisation of PEEP [57]. However, the potential clinical benefits of these approaches still await confirmation in RCTs, while debate regarding the best way to set PEEP in individual patients remains ongoing [58–60], reflecting the complexity of the underlying problem. Roth *et al.* developed a patient-specific modelling approach capable of predicting the physiological effects of changes in ventilator settings by integrating EIT with computational lung modelling, providing a pathway for constructing personalized models informed by regional ventilation data rather than relying solely on global airway signals [61].

Patient-specific models have provided insights into the mechanistic basis for RCT-derived associations between VILI indicators such as driving pressure and mortality [62], allowed different VILI indicators to be compared in terms of their suitability as 'targets' for maximally protective ventilation [63], and provided direct quantitative comparisons of hemodynamic effects of different recruitment manoeuvres on patients with differing severities of ARDS [64]. Other studies have demonstrated the ability to predict lung mechanics during recruitment manoeuvres in volume- or pressure-control ventilation modes [65,66].

Patient-Specific Mechanistic Models to Evaluate Different Modes of Mechanical Ventilation:

Recent work has leveraged the capability of computational tools to enable direct comparison of different ventilation strategies under identical conditions free from the confounding effects of environmental variability that inevitably limits clinical trials. This capability is particularly useful in evaluating novel or non-standard modes of mechanical ventilation, as it allows a precise and reproducible quantification of their advantages and limitations relative to current standards of care. In Joy *et al.*, a cohort of patient-specific models was created using a dataset consisting of pairs of ventilator settings and arterial blood gases recorded in 98 patients with ARDS receiving pressure-controlled ventilation (PCV) [67]. Each model was then simulated with ventilator settings changed to those typically used in airway pressure release ventilation (APRV), an alternative modality of IMV currently used in selected patients and whose role and merits as a primary mode of ventilation are the subject of current investigations [68,69]. By measuring all relevant VILI indices in the same models during simulations in each ventilator mode, a precise comparison of the relative lung-protective effects of APRV versus PCV could be obtained. Exploiting the power of computational simulation, the authors then applied advanced optimization algorithms to evaluate more than 4.8 million changes to these ventilator settings to identify the lowest possible values of VILI indices that could theoretically be achieved in both modes while preserving adequate gas exchange. This analysis showed that typical APRV settings were close to optimal in terms of reducing mechanical power and mean tidal alveolar recruitment/de-recruitment, both of which were more than 30% lower compared with the documented PCV settings, at the cost of moderate hypercapnia.

These results highlight the potential of patient-specific mechanistic models to augment and inform the design of clinical trials of other novel or non-standard ventilator modes, such as neurally adjusted ventilatory assist (NAVA) [70] and flow-controlled ventilation (FCV) [71]. APRV, NAVA and FCV all differ in fundamental ways from each other, and from standard ventilator modes, and all have demonstrated potential benefits in animal studies and preliminary studies in patients [4,72,73]. However, there is a lack of detailed evidence with which to directly compare them to standard modes, and significant uncertainty regarding how, and in which patients, they should be deployed. Patient-specific mechanistic models could help address this challenge by (a) allowing direct and noise-free comparisons of VILI and other key indices against standard modes, (b) facilitating development of optimized settings and implementation protocols for the novel ventilation modes, and (c) identifying particular patient sub-groups who would most benefit from each mode for targeting in future RCTs. Outside of the context of fully controlled IMV, patient-specific mechanistic models could support understanding of patient-ventilator asynchronies in assisted ventilation where monitoring becomes more challenging, and could help to determine the key pathophysiological mechanisms during transition phases such as ventilator weaning and extubation, although work in these areas is still in its infancy.

Patient-Specific Mechanistic Models to Advance Closed-Loop Mechanical Ventilation:

The task of adjusting mechanical ventilator settings seems theoretically amenable to being largely automated via closed-loop control algorithms, at least in the ‘steady-state’ where a patient is stable and only minor adjustments are required (analogous to aircraft autopilots removing the need for airline pilots to directly fly the plane during the cruise). Although various closed-loop ventilator modes have been available for some time [74], they have arguably not demonstrated the ability to deliver the improvement in patient outcomes that would lead to their widespread adoption [75]. For example, almost all target oxygenation, when current clinical practice is focused on minimising the risk of VILI, and few attempt to make use of all available ventilator settings. Recent developments in the field of control engineering, driven by machine learning, are producing powerful new approaches such as model-predictive control and reinforcement learning, that can incorporate clinical expertise and may be ideally suited to meeting these challenges [76-78]. Patient-specific mechanistic models could have an important role to play as surrogate patients for the development, training and testing of next-generation automated ventilation systems [79,80], analogous to the way in which aircraft manufacturers currently design and exhaustively test novel closed-loop flight control systems on detailed aircraft simulation models before conducting actual flight tests in real aircraft [81].

Digital Twins for On-Line Clinical Decision Support:

Beyond their use as tools for off-line medical research, the ultimate destination for patient-specific computational tools will be to create fully-fledged digital twins of patients receiving mechanical ventilation, where they could potentially be used at the bedside for advanced patient monitoring and real-time clinical decision-support. The ability of state-of-the-art simulators to accurately predict key responses of individual patients to changes in ventilator settings [82] offers the possibility of clinicians being able to quickly simulate proposed changes in a bedside digital twin and check the predicted responses against their expectations before implementing the changes on the ventilator. Going one step beyond this, decision-support systems could be designed based on a patient's digital twin to constantly monitor their state in real-time and suggest changes to the ventilator settings in case of clinical improvement or deterioration. Although experience with clinical trials of on-line decision support systems has thus far been mixed [83], this may be due to restrictions on the complexity of the underlying models that could be implemented computationally at the bedside, and to human factors related to clinician trust and expertise in using these systems. Both these challenges to adoption in clinical practice will likely ease as computational algorithms are further refined, the computational power available at the bedside continues to expand, clinicians gain experience and expertise with using decision support systems, and these systems are increasingly embedded directly within ventilators rather than implemented as stand-alone tools.

Ventilation of Neonatal and Paediatric patients

Background and Clinical Challenges:

Mechanical ventilation in neonates and children differs fundamentally from adult ventilation due to developmental differences in lung structure, chest wall mechanics, respiratory control, airway dimensions, haemoglobin physiology, disease pathology and cardiopulmonary coupling [84,85]. Preterm neonates in particular exhibit highly compliant chest walls, small and easily collapsible airways due to surfactant deficiency, low functional residual capacity, and reduced pulmonary compliance in common conditions such as neonatal respiratory distress syndrome (RDS) [84,85]. In children, the range of lung sizes and disease phenotypes encountered in paediatric intensive care units (PICUs) is exceptionally broad, spanning bronchiolitis and pneumonia through to paediatric acute respiratory distress syndrome, neuromuscular weakness, and congenital heart disease [86,87]. These factors contribute to marked inter-patient variability in responses to ventilator settings and to a persistent tension between achieving adequate gas exchange and avoiding VILI [86]. At the bedside, these challenges are compounded by practical constraints on measurement, including difficulties in obtaining repeated arterial blood gases, uncertainty in the interpretation of capnography in small lungs with variable dead space, and frequent leaks around uncuffed tubes or interfaces that degrade the reliability of delivered tidal volume and pressure measurements [88]. These features make neonatal and paediatric ventilation a compelling target for digital twin approaches that can integrate sparse measurements with mechanistic understanding to infer unmeasured physiological states and predict responses to alternative ventilator strategies.

Patient-Specific Mechanistic Models in Paediatric Ventilation:

Early work relevant to lung modelling approaches applicable to paediatrics was published in 1977 by C.J. Dickinson. *MacPuf* was a pioneering computer simulation model designed for teaching, research, and clinical use to study human respiration, gas transport, and acid-base balance [89]. Flechelles *et al*. later updated and extended this model with a visual interface [90]. However, both the original and updated models suffer from several limitations. These include representing the entire lung as a single compartment, specifying a lower age limit of 8 years, lacking the ability to represent the pathophysiology of individual patients or disease states, and not attempting to validate model responses against real patient data.

More recent studies using mechanistic models of paediatric patients have explored how candidate lung-protective targets should be prioritized when selecting ventilator settings in children versus adults. Saffaran *et al*. performed a computational investigation comparing strategies based on driving pressure and multiple formulations of mechanical power in mechanistic models of adult and paediatric ARDS patients [63]. Their analysis highlighted that the choice of optimisation target can materially alter the derived protective settings, and that strategies that reduce one injury-related metric may increase another, for example, through increases in tidal volume when minimising mechanical power. This illustrates a key advantage of mechanistic models in paediatrics - they enable systematic comparisons of competing protective objectives while explicitly accounting for paediatric-specific mechanics and scaling, without requiring large and costly interventional trials in vulnerable patient groups.

Patient-Specific Mechanistic Models in Neonatal Ventilation:

Patient-specific models of neonatal patients have also recently begun to emerge. Saffaran *et al*. reported the development of mechanistic models of mechanically ventilated preterm neonates with RDS using a high-fidelity cardiopulmonary physiology simulator adapted to neonatal physiology, including lung mechanics, dead space, pulmonary vascular resistance, oxygen consumption, and the oxygen affinity of foetal haemoglobin [91]. Using multiple time-point data from 11 preterm infants receiving volume-controlled ventilation, the authors calibrated each model to reproduce arterial blood gases and airway pressures, then demonstrated high accuracy not only for the calibrated outputs but also for additional uncalibrated variables. This study is important for two reasons. First, it demonstrates the feasibility of creating patient-specific mechanistic models which reproduce clinically observed trajectories, despite the sparse and noisy data typical of neonatal intensive care. Second, it provides a concrete platform for ‘simulate before treat’ testing of alternative ventilator settings in a domain where small changes in delivered pressure or volume can have disproportionately large consequences, and where clinicians are often balancing competing risks of volutrauma, atelectrauma, hypocapnia-related brain injury, and oxygen toxicity. These tools could help address the rising incidence of bronchopulmonary dysplasia (BPD) in the preterm population that often results in life-long respiratory disease in the form of asthma, chronic respiratory infections, and chronic obstructive pulmonary disease in adults [92,93].

Patient-Specific Mechanistic Models to Advance Closed-Loop Neonatal/Paediatric Ventilation:

Neonatal and paediatric critical care have long been early adopters of automated and closed-loop ventilator control, particularly for oxygenation, because titrating inspired oxygen to maintain saturations within a target range is frequent, labour-intensive, and safety-critical in these patients. Closed-loop automated oxygen control (CLAC) systems that adjust the fraction of inspired oxygen (FiO_2) based on continuous pulse oximetry (SpO_2) monitoring have progressed to randomized trials in ventilated infants. For example, Kaltsogianni *et al*. recently reported an RCT in preterm ventilated infants comparing CLAC with manual oxygen control which found that CLAC was associated with reductions in the durations of mechanical ventilation and supplemental oxygen, the need for home oxygen and the incidence of BPD [94]. Patient-specific mechanistic models could advance research in this direction by predicting the consequences of oxygen titration decisions on carbon dioxide clearance, lung recruitment, and haemodynamics, thereby supporting more holistic control strategies beyond SpO_2-only regulation.

Closed-loop control of carbon dioxide is arguably an even stronger candidate for integration of mechanistic models, because arterial carbon dioxide tension ($PaCO_2$) is a key determinant of cerebral blood flow and brain injury risk in preterm infants [95], yet it is difficult to measure continuously and is influenced by both ventilator settings and spontaneous breathing. Proof-of-concept work has demonstrated physiological closed-loop CO_2 control in neonatal-relevant experimental settings. Buglowski *et al*. described a cascaded controller that regulates arterial CO_2 by estimating $PaCO_2$ from end-tidal CO_2, with feasibility demonstrated in both a mathematical patient model and *in vivo* lamb experiments [96]. Building on this, Pfannschmidt *et al*. reported closed-loop control of arterial CO_2 for neonatal mechanical ventilation with *in vivo* interaction with spontaneous breathing, reflecting the reality that neonatal patients frequently breathe spontaneously and asynchronously with the ventilator [97]. These studies highlight a natural role for patient-specific mechanistic models - by fusing capnography, airway signals, and intermittent blood gases within a physiological framework, they could provide improved real-time estimation of arterial CO_2 (and other latent variables such as alveolar ventilation and dead space fraction), increasing the safety of closed-loop ventilation and potentially reducing the burden and risks associated with frequent arterial sampling.

Data-Driven Models to Predict Treatment Outcome in Neonatal/Paediatric Patients:

AI and machine learning methods are increasingly being applied to develop data-driven models that can predict clinical responses to respiratory support in neonates and children. These predictive models aim to assist clinicians in anticipating treatment outcomes such as extubation success, or HFNC/NIV failure, and the need for escalation to IMV, thus enabling earlier and more personalized interventions [98,99].

In neonatal care, accurate and early prediction of readiness for extubation is particularly important because premature infants exposed to prolonged mechanical ventilation are at heightened risk of BPD and other sequelae. Traditional clinical predictors have shown limited accuracy in forecasting extubation outcomes, motivating the development of AI-based approaches [98]. Several studies have developed machine learning models to predict extubation outcome in low birthweight or preterm neonates using combinations of demographic, ventilator, vital sign, and clinical data. In a large cohort of low birthweight neonates, Natarajan *et al*. reported that boosted-tree machine learning models incorporating demographics, ventilator parameters, and medications achieved AUC values of 0.82 for predicting reintubation within 7 days of extubation [100]. Similarly, Tao *et al*. used XGBoost machine learning models to predict extubation outcome in neonates with BPD, identifying partial pressure of oxygen (PO_2), FiO_2, and ventilator rate as key predictors, with good discriminative performance [101]. Prospective work by Brasher *et al*. demonstrated that combining pulse oximetry and continuous ventilator monitoring data in preterm infants can yield AUCs for predictions exceeding 0.80, particularly when stratified by postnatal age, highlighting the value of dynamic physiological signals for improving predictive accuracy beyond static clinical variables [102].

Broader reviews of the use of AI in neonatal medicine emphasize that models predicting respiratory treatment response, including extubation readiness, drug dosing to reduce ventilation duration (e.g. caffeine and postnatal corticosteroids), and short-horizon prediction of ventilation parameters, consistently show promise but remain limited by small datasets and scarce external validation [98]. In parallel, interest is growing in using AI to predict NIV failure in neonates. A focused review by Jeffreys *et al*. identified multiple AI-based approaches for predicting NIV failure in the neonatal unit, with reported AUCs frequently exceeding 0.80 and key predictors including gestational age, SpO_2, and maximum FiO_2 [99].

In PICUs, data-driven models have also been developed to improve the prediction of extubation failure. Rooney *et al*. applied machine learning to high-frequency physiological data from children in a paediatric cardiac ICU and demonstrated that variables such as dynamic compliance, heart rate, and oxygenation extremes were strongly associated with extubation outcomes [103]. More recently, Digitale *et al*. proposed an expert-augmented machine learning framework for predicting extubation readiness in the PICU, showing improved generalisability across test sets when clinician insight was integrated with algorithmic modelling [104]. These approaches illustrate the feasibility of dynamic prediction of ventilation outcomes in heterogeneous paediatric populations and underscore the importance of combining physiological data streams with clinical domain knowledge.

Challenges and Opportunities in Neonatal/Paediatric ARF:

Despite this progress, major challenges remain for the development of neonatal and paediatric patient-specific computational tools. Mechanistic models must address age-dependent parameterisation, rapid physiological changes over time (including growth, disease evolution, and treatment effects such as surfactant), and the substantial impact of leaks and interface artefacts on measured airway signals. Data-driven prediction models face familiar issues of dataset shift across centres, device-specific measurement differences, and the need for clinically meaningful interpretability in high-stakes decisions. Relying solely on AUC is also insufficient for highly demanding clinical environments such as the NICU and PICU. For example, predictive models for patient risk identification (screening models) may prioritize sensitivity, whereas ventilator mode adjustment models would require high specificity and reliability. However, these challenges also highlight clear opportunities. In neonates, personalized mechanistic models that explicitly represent the unique element of foetal haemoglobin oxygen transport, pulmonary vascular transition physiology, and shunt dynamics could enable more faithful prediction of oxygenation responses than adult-derived models. In children, mechanistic models that integrate regional information from EIT and incorporate spontaneous breathing effort could help to quantify injurious patient-ventilator interactions and support lung- and diaphragm-protective strategies. Across both domains, integrating AI-based predictive models with personalized mechanistic models may offer a powerful hybrid approach, combining longitudinal physiological simulation with data-driven risk stratification to optimize respiratory care and improve patient outcomes. Ultimately, neonatal and paediatric ventilation sits at the intersection of high physiological complexity and constrained opportunities for large interventional trials, precisely the setting in which patient-specific computational tools could deliver the most benefit – providing urgently required models that can accurately predict responses to changes in respiratory support, expedite weaning decisions, and personalize treatment strategies in vulnerable neonatal and paediatric patients.

Pre-Hospital and Immediate Ventilation

Background and Clinical Challenges:

While computational models and, more recently, digital twins, have been utilized in pre-hospital contexts for several years to investigate resource allocation [105–111], the application of such models to investigate any medical intervention in the field appears exceedingly rare. This is likely due to the obvious difficulties in assembling comprehensive patient datasets from pre-hospital encounters – an issue researchers have long recognized as repressing innovation in the area [111,112]. Indeed, within the context of pre-hospital ventilation strategies, there appear to be few instances in the literature of patient-specific computational tools being utilized to examine best practice. Instead, what literature does exist utilizes mechanistic models either of animals used in pre-clinical experimental studies or of generic virtual patients created by combining multiple partial datasets.

Mechanistic Models of Animals:

This approach is exemplified by the work of Mistry *et al.*, who adapted an existing model of the human cardiopulmonary system to represent the physiology of pigs, and used this to create mechanistic models of individual porcine research subjects [113,114]. Once calibrated against detailed physiological data from animal experiments, the authors used their models of pigs to investigate the efficacy of pre-hospital CPAP following either primary blast lung injury with hypovolemic shock or phosgene-induced chemical lung injury. Though both these types of lung injury can occur as a result of isolated industrial accidents, they may also occur during mass casualty events, which can overwhelm medical systems if suitable pre-hospital treatment is not implemented. CPAP has long been investigated as a potential pre-hospital ventilation strategy, especially after mass-casualty events, given the relatively non-specialist knowledge required to initiate therapy.

Using porcine mechanistic models, Mistry *et al*. explored the efficacy of CPAP following blast lung injury and hypovolemic shock at varying injury and pressure levels, and found that CPAP greater than 5-10 cmH_2O did not produce a clinical benefit because of pressure-induced haemodynamic compromise [113]. In a follow-up study, they also investigated not only the gross efficacy of CPAP following phosgene-induced lung injury, but also the physiological impact of therapeutic adaptations associated with pre-hospital deployment [114]. They found that delays in initiating CPAP were associated with reduced improvements in oxygenation, but that clinically relevant benefit was still generated even when CPAP was initiated up to 8 hours after exposure. They also found that CPAP levels beyond 5 cmH_2O produced only a small additional benefit, but inclusion of low-flow oxygen – something that is readily available in the field, significantly increased median PaO_2 at all pressure levels. Both studies suggest that CPAP is a beneficial mode of pre-hospital support for patients with combined blast and hypovolemic shock and phosgene-induced lung injury, and one that can be adapted to reflect available pre-hospital resources while maintaining clinical benefit. This work highlighted the role that mechanistic models can play in refining data derived from animal experiments by extrapolating from their results to evaluate additional/alternative interventions, reducing and potentially ultimately replacing animals in this area of research.

Mechanistic Models of Virtual Patients:

As an alternative approach, some researchers have chosen to create models of virtual patients (as opposed to models of specific individuals) by combining multiple partial datasets. This technique is itself an evolution of previous modelling methodologies used in cases of limited data availability, where models have utilized published ranges for unmeasured parameters [115,116] or even combinations of human and animal data [117,118]. A successful example of this approach is the work of Daudre-Vignier *et al.*, which combined three separate data sources to create a cohort of ten virtual human patients suffering from cardiac arrest [119]. Using these virtual patients, they then investigated the potential benefits of modifications to existing guidelines for cardiopulmonary resuscitation, including potential changes in ventilatory support. Their results indicated that, when compared to American Heart Association guidelines, a more conservative ventilation strategy may improve clinical outcomes by reducing pressure-induced haemodynamic compromise.

Overall, despite continuing constraints due to the lack of detailed patient datasets, recent studies show a clear evolution towards the more widespread use of patient-specific computational tools in pre-hospital respiratory support. Despite their historical and ongoing value in advancing physiological understanding, animal studies have limited capacity to inform the day-to-day management of individual patients. Species-specific differences, experimental constraints, and the controlled nature of animal models mean that findings often translate only indirectly to the heterogeneous, dynamic conditions encountered in clinical practice in humans. In contrast, patient-specific computational models offer the ability to explore physiological responses and therapeutic strategies at the level of the individual patient, integrating available data to test alternative interventions under clinically relevant conditions. This capability positions them as a complementary, and increasingly practical, tool for bridging the gap between experimental research and personalized clinical decision-making, particularly in contexts where traditional experimental approaches are constrained or insufficient. As governments, funding and regulatory agencies intensify efforts [120–123] to refine, reduce, and replace animal (and particularly non-human primate and large-animal) experiments, this capability looks set to become increasingly important.

Discussion

Current Limitations and Implementation Challenges:

Several limitations and challenges remain to be addressed before patient-specific computational tools can be widely adopted in clinical practice. At the most fundamental level, there are currently no agreed standards defining how closely, and in what manner, computational models must replicate a patient's disease state for it to be considered a validated clinical surrogate suitable for evaluating treatment strategies. In the case of data-driven predictive models, the required level of accuracy of the underlying machine learning models is also currently an open question. It is unclear whether performance should be judged against an absolute threshold (for example, an AUC $\geq$ 0.80) or whether demonstrating improvement over currently used clinical indices is sufficient. The substantial differences in predictive accuracy often observed between internal and external validation of machine-learning models highlight persistent challenges in generalisability.

This also highlights the need for rigorous multi-centre and prospective external validation, the development of standardized evaluation benchmarks, and testing for robustness to dataset shift and inter-centre variabilities. Other limitations of some machine learning models, such as their computational cost, challenges in interpretability, and risks of hallucinations, also need to be addressed to ensure clinical and regulatory acceptance [124]. To be used in real-time, digital twins for at-the-bedside decision support systems should also dynamically reflect temporal changes in a patient's disease state and encompass bidirectional information flow between the patient and their twin (without requiring additional non-routine measurements). However, work on developing such dynamic digital twins in the context of ARF is in its infancy.

Issues around ensuring de-identification and ethical sharing of detailed individual patient data are also a major challenge, as researchers attempt to create ever larger datasets to train more accurate models. Datasets that are used for model development must be interrogated to remove any potential demographic and institutional biases. As the number of validated models grows, there will be an increasing need for dedicated, open-source biobanks on which they can be stored, shared and re-used by the wider community, for example for *in silico* clinical trials. Governmental and transnational initiatives to develop appropriate frameworks for data infrastructure and governance, along with pragmatic and open collaboration between clinicians, patients, and engineers, will be essential to address these challenges.

At the healthcare systems level, patient-specific computational tools will need to be incorporated into routine clinical workflows and integrated within hospital's electronic healthcare records. At the bedside, it is currently unclear whether ventilator manufacturers will integrate such tools into next generation ventilators, or whether stand-alone systems will be developed by new companies. Infrastructure requirements and human factors associated with the use of these new technologies will also need to be carefully considered, as will issues around transparency and responsibility in the case of adverse outcomes. Finally, since fully-fledged digital twins are likely to be classified as medical devices, regulatory hurdles concerning validation and verification requirements, data governance, cybersecurity, liability, will need to be met by any such system before clinical implementation. The fact that the Beacon Caresystem [83], which uses mechanistic models to provide ventilator decision support, has been granted approval from the US FDA is a promising indication that these hurdles are not insurmountable.

Future Outlook:

Several future trends are discernible from this review of the current state of the art in applying patient-specific computational tools in the context of acute respiratory failure. The availability of greater and ever cheaper computing power, combined with large-scale international adoption of electronic patient health records, will facilitate the creation of increasingly complex multi-organ models that can be applied in real-time at the bedside. How exactly these will be used by clinicians remains unclear, but a 'simulate-before-treat' approach would seem to be a logical first step, with clear potential clinical benefits, and minimal ethical hurdles due to full preservation of the clinician's decision-making authority. Once patients' and clinicians' confidence in the reliability and accuracy of these tools is sufficiently strengthened through clinical experience, decision support systems with progressively greater levels of automation could be introduced, with the aims of both improving treatment of patients and reducing the workload of clinicians. Importantly, for a variety of reasons, we see little prospect of these technologies replacing clinicians at the bedside in any meaningful way, particularly in the context of Critical Care; the lesson from passenger aircraft (which have had the technological capability to fly reliably without pilots for many years) is that when human beings feel most vulnerable and are threatened by life-or-death scenarios, they will insist on having another human in charge of their care. The fundamental importance of keeping a 'human in the loop' is increasingly being realized even in domains that have traditionally employed a high degree of automation, with the primary focus of the Industry 5.0 framework being to integrate innovative AI technologies with human actors, to ensure that production is not only digitalized but is also resilient, sustainable, and human-centric [125].

In the context of medical research into novel ventilation strategies, the availability of ever-larger cohorts of fully validated patient-specific mechanistic models will inexorably shift pre-clinical research away from animal experiments. The fidelity of ever more complex computational models to human physiology will inevitably continue to increase in tandem with the increase in available patient data, while the fidelity of animal models will not, and at some stage a tipping-point will arrive at which the credibility of experiments in computational models is judged by clinicians to surpass that of *in vivo* experiments in animal models. At that point, the cost, ethical, practical and time advantages associated with computational approaches will become overwhelming. The use of mechanistic models to help design, extract additional data from, and at least partly replace RCTs in patients also looks certain to increase, with potentially important implications for research in

Critical Care, where such trials are particularly difficult. This process is already well underway in other fields of medicine, with the global *in-silico* clinical trial market forecast to exceed $5.6 billion by 2030 [126].

Glossary

Term	*Explanation*
Data-Driven Prediction Model	A computational model, based on the application of machine learning to large-scale patient datasets, that can be used to predict a patient's responses to specific treatment interventions
Patient-Specific Mechanistic Model	A computational model, based on known physical, chemical, and biological laws, that has been shown to accurately replicate detailed data from an individual patient
Digital Twin	A patient-specific and predictive model which is dynamically updated in real-time, with continuous bidirectional interaction between the patient and the digital twin, for example in the context of bedside decision support
Decision Support System	A digital tool designed to improve healthcare delivery by providing clinicians with timely, patient-specific information and suggested treatment options.
In-Silico Clinical Trial	A clinical trial of a drug, medical device, or treatment intervention that is carried out using patient-specific mechanistic models rather than actual patients

Declarations

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Not applicable

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Not applicable

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Not applicable

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The authors declare that they have no competing interests.

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