memory/effector T cells: IL-17A and tumor necrosis factor [TNF]-α; γö T cells: IL-17A and IL-22) and carried out a similar analysis here. This analysis suggested that while VML injury was associated with both pathogenic and non-pathogenic Th17 cells and this phenotype persisted in ECM+E-STIM wounds, this was not observed in ECM-treated wounds.

Conclusion

This is the first comprehensive analysis of tissue inflammatory mediators in the context of experimental VML injury and the impact thereon of perturbations that may alter the wound healing phenotype, suggesting a role for Th17 cells.

doi:10.1016/j.jcrc.2024.154962

Network analysis of single-nucleotide polymorphisms (SNPs) associated with aberrant inflammation in trauma patients suggests a role for programs involving CD55 and delineates novel SNPs associated with a Type 17 immune phenotype

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Introduction

Critical illness stemming from severe traumatic injury is a leading cause of morbidity and mortality worldwide, and involves the dysfunction of multiple organ systems, driven, at least in part, by dysregulated inflammation. We and others have shown a key role for genetic predisposition to dysregulated type 17 immune responses and downstream adverse critical illness outcomes. Recently, we demonstrated an association among genotypes at the single-nucleotide polymorphism (SNP) rs10404939 in LYPD4, dysregulated systemic inflammation, and adverse clinical outcomes in a broad sample of ~1000 critically ill patients. In a related analysis, we identified a number of rare SNPs associated with altered systemic inflammation. Here, we examined these datasets using novel bioinformatics methods to define networks of interaction.

Methods

We focused the present study solely on trauma-associated critical illness. We first sought to gain mechanistic insights into the role of LYPD4 in critical illness by bioinformatically analyzing potential interactions among rs10404939 and other SNPs. We analyzed a dataset of common (i.e., not rare) SNPs previously defined to be associated with genotype-specific, significantly dysregulated systemic inflammation trajectories in a dataset 380 trauma survivors, in comparison to a control dataset of common SNPs determined to exhibit an absence of genotype-specific inflammatory responses. Next, we utilized similar methodology to define networks of interaction among rare SNPs (i.e., those present in 5–10 % of patients).

Results

In the control dataset, this analysis implicated SNPs associated with phosphatidylinositol and various membrane transport proteins, but not LYPD4. In the patient subset with genotypically dysregulated inflammation, our analysis suggested the co-localization to lipid rafts of LYPD4 and the complement receptor CD55, as well as the neurally related CNTNAP2 and RIMS4. Segregation of trauma patients based on genotype of the CD55 SNP rs11117564 showed distinct trajectories of organ dysfunction and systemic inflammation despite similar demographics and injury characteristics. Subsequent analyses also implicated RAR related orphan receptor A (RORA) and the PIKFYVE complex downstream of phosphatidylinositol metabolism, both central to the differentiation of Th17 cells.

Conclusions

Collectively, these analyses define novel interactions among SNPs that extend and unify prior studies pointing to aberrant activation of type 17 immunity in trauma-associated critical illness.

doi:10.1016/j.jcrc.2024.154963

Optimal timing for renal replacement therapy in critically ill patients using reinforcement learning algorithms

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Introduction

Acute kidney injury (AKI) is a prevalent and severe condition in critically ill patients, with high mortality and morbidity rates. The range of options for AKI is limited, with the majority of interventions focusing on supportive measures. Renal replacement therapy (RRT) is frequently necessary to address the acute metabolic disturbances and fluid imbalances that arise in AKI. The optimal timing for initiating RRT in AKI remains a topic of discussion, particularly in the absence of absolute indications. Recent studies indicate that early initiation of RRT may not result in improved survival outcomes and may potentially lead to additional complications. This underscores the necessity for a more personalized approach to RRT timing. This study aims to explore the use of reinforcement learning (RL) algorithms to determine the optimal timing for RRT in critically ill patients.

Methods

The objective of this study is to employ a RL algorithm to analyse ICU clinical data and identify the optimal timing for initiating RRT patients with AKI. The dataset, presented as a four-hour multidimensional time series, comprises patient characteristics, clinical parameters, and treatment trajectories. The preprocessing stage entails the handling of missing data followed by the application of a normalisation process. The RL algorithm was trained on ICU data from the MIMIC-IV v2.2 database, with 90-day mortality serving as the reward signal and RRT dosage as the action space. The data was partitioned into three subsets: 70 % for training, 20 % for validation, and 10 % for testing. The efficacy of a range of RL algorithms, including actor-critic models, were evaluated using a high-confidence off-policy evaluation methodology. External validation will be conducted using the data of General Hospital of Vienna with the objective of comparing the performance of the RL algorithm against actual clinician decisions.

Results

After applying the exclusion criteria, the resulting dataset comprised 31,269 ICU patients from the MIMIC-IV v2.2 database, which was transformed into a format suitable for RL algorithms. The preliminary findings from off-policy evaluation methods, which estimate the 95 % lower bound, suggest a potential reduction in 90-day mortality rates and may also indicate a possible reduction in the length of ICU stays when RL algorithms were used for initiation timing, compared to the timing used by human clinicians. These off-policy evaluation methods demonstrated robustness in various tests.

Conclusions

Preliminary results from this study suggest that RL algorithms could potentially optimise the timing of RRT in patients with AKI, potentially reducing 90-day mortality and ICU stay compared to traditional clinician-driven timing. External validation, yet to be completed, will further establish the effectiveness of these algorithms. These results support the continued exploration and refinement of RL-driven approaches for personalised treatment strategies in critical care.

doi:10.1016/j.jcrc.2024.154964

Modeling organ crosstalk and cellular adaptation in response to clinical intervention during multiple organ dysfunction syndrome

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Introduction

Multiple organ dysfunction syndrome (MODS) is the leading cause of death in the intensive care unit (ICU). The dysfunction of a single organ disrupts complex organ interactions leading to the onset of MODS. These interaction mechanisms are not well understood, which has limited development of targeted interventions. Most interventions alleviate stress on the organs, but do not address the underlying cause. To better understand these mechanisms, we expanded our previous organ failure model to include interventions impacting organ and cell level response. The model integrates a game theoretic approach for cellular adaptation with a physiological model incorporating the immune system, multiple organs and trafficking of multiple currencies.

Methods

Our previous lung-centric model was expanded to incorporate liver and kidney interactions. The lung is responsible for oxygen uptake, while the liver and kidney clear wastes. The immune system consists of 8 states: pathogen, lung and systemic pro- and anti-inflammatory responses, and damage to each organ. Lung specific inflammation is used to simulate a pathogen insult in the lung, where the local response causes lung damage and can trigger systemic inflammation and liver and kidney damage. Lung injury causes a decrease in oxygen availability, while kidney and liver injury cause systemic waste accumulation. The trafficking of these currencies (oxygen, wastes) inform the physio-economic game. Cells have two strategies: cooperation and defection. Each strategy has a set of reward functions for each currency. Cells transition between strategies to maximize an organ's reward and adapt to changes in currency concentration, but significant defection leads to further dysfunction. To prolong survival and promote recovery, a series of interventions were designed to address the pathogen, excessive inflammation, and organ dysfunction. Mechanical ventilation is implemented as a logic controller. Supplemental oxygen and positive end expiratory pressure (PEEP–increases lung volume for gas exchange) are used to maintain a target oxygen saturation. Dialysis is implemented as a first order clearance rate applied for a set time interval at a given frequency to reduce kidney waste. The administration of a generic antibiotic and anti-inflammatory are each implemented using a one-compartment model.

Results

The model predicts a recovery envelope in two-dimensional inflammatory parameter space (pro- vs anti-inflammatory generation), with MODS occurring outside this envelope. In both recovery and failure, lung damage decreases oxygen delivery and incentivizes cellular defection as a protective mechanism in the liver and kidney. During failure, the positive feedback loop between oxygen, waste, and organ dysfunction overwhelms the protection mechanisms. If inflammation is severe, it damages the liver and kidney, and in combination with defection causes systemic waste accumulation. The progression of MODS is also dependent on the initial location of the pathogen insult. If the pathogen is systemic, triggering lung and systemic inflammation, this shifts the main driver of dysfunction from only oxygen towards a combination of waste accumulation and oxygen deficiency. To avert collapse interventions can be applied to increase oxygen availability, waste clearance and pathogen elimination. This increases the recovery envelope, where its size is dependent on the interventions used, their timing and magnitude. The predicted progression of MODS across this parameter space is compared to trends in ICU patient biomarkers and critical care scoring systems.

Conclusions

Our model framework was expanded to produce a multi-organ, multi-currency, physio-economic game that integrates cell and organ level functions. The predicted progression of MODS captures the impact of organ interdependencies and clinically observed outcomes. The use of interventions creates the foundation for further investigation of improved patient outcome through individualized modulation of the treatment plan.

doi:10.1016/j.jcrc.2024.154965

Control-oriented predictions of candidate coagulation protein therapies for invasive pulmonary aspergillosis

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Introduction

Invasive pulmonary aspergillosis is a severe form of pneumonia that primarily affects immunocompromised individuals, including cancer chemotherapy patients and transplant recipients. Despite