Specialized health utilization, child health ability, and personalized-precision medicine.

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Research agenda

Investigate the relationship between *health status* and *health utilization*.

- Work towards defining health status via:
- (i) Precision medicine (ii) Personalized medicine.
- To determine an optimal level of health utilization.
- In a medical environment (pediatric intensive care unit PICU) where health utilization is high value and resource intensive.

Roadmap

- Motivate with an *economic model* of PICU health utilization and child health status.
- Develop an *econometric* framework for existing severity scores within the PICU.
- *Clinical analysis* using a prospectively collected multi-centre observational data set.
- Propose a *precision medicine* framework within the PICU.

Medical research environment and study population

- Pediatric Intensive Care Units (PICU)
- Critically ill children - age - newborn to eighteen- requiring immediate and often life-saving care.
- High levels of acuity and physiologic instability.
- Heterogeneous syndromes rather than disease specific.
- Time sensitive environment with rapidly changing clinical trajectories.

High value care

- Exceptional decline in mortality over the past 40 years.
- Approximately 2-5% from 30-40%.
- As compared to adult units with approximately 30% mortality despite lower levels of physiologic instability.
- Human capital approach suggests early interventions have long term consequences-both good and bad.

Resource intensive

- PICU is characterized by multi-disciplinary care teams: Nursing, Respiratory therapists, Intensivists, Specialist consultants.
- One-to one nursing with individual care rooms.
- Advanced diagnostics and monitoring.
- Technologically dependent and advanced therapies: mechanical ventilation, extracorporeal life support (ECLS).
- High risk therapies and interventions with possibly unknown therapeutic efficacy.

Economic model of pediatric intensive care

- Adapt a stylized model of health utilization to reflect PICU setting[1].
- Patient demand, physician supply, and regional constraints (multi-centre study).
- Patient demand is based on a patient's need: Primary goal from all perspectives is to recover a child's health.
- Patient demand is not determined by preferences or tastes.

[1] (Finkelstein, Gentzkow, & Williams, 2016)

Notation and assumptions

- $i = 1..N$ children in a country with $g = 1...G$ geographic regions.
- Child's latent health stock: $\tilde{\theta}_i^H \in \mathbb{R}$.
- Admission to PICU: $a_i \in \{0, 1\}$
- In general, admission to PICU: $(0 \leq \mathbb{P}(a_i = 1|\tilde{\theta}_i^H) \leq 1)$.
- However, some admissions are accidental (i.e. pediatric trauma): $(0 \leq \mathbb{P}(a_i = 1) \leq 1)$.

Event health status: $h_i(\tilde{\theta}_i^H)$

- A child's event *health status*, $h_i(\tilde{\theta}_i^H) \in \mathbb{R}$, is a function of their health stock and captures the severity of exposure to a health related event resulting in admission to PICU.
- Higher values of $\tilde{\theta}_i^H$ represent worse health.
- $h_i(\tilde{\theta}_i^H)$ increasing in $\tilde{\theta}_i^H$ at a decreasing rate.
- $h_i'(\tilde{\theta}_i^H) > 0$ and $h_i''(\tilde{\theta}_i^H) \leq 0$.

Patient demand: Two components

- A child will benefit from a quantity of intensive care, $y_i \in \mathbb{R}^+$ that is matched to their severity of exposure $h_i(\tilde{\theta}_i^H)$.
- A child will benefit from a quantity of care that is proportional to their underlying health stock $\tilde{\theta}_i^H$.
- Combined, a child's benefit from intensive care:

$$\mathcal{U}(y_i|h_i, \tilde{\theta}_i^H) = -\frac{1}{2}(y_i - h_i(\tilde{\theta}_i^H))^2 + \tilde{\theta}_i^H y_i, \tag{1}$$

Motivating precision medicine

- Optimal condition $y_i = h_i(\tilde{\theta}_i^H)$.
- Equate the need for health care with degree of severity[2].
- Medical technology may not yet be developed for extreme or unusual levels of illness. $h_i'(\tilde{\theta}_i^H) > 0$ and $h_i''(\tilde{\theta}_i^H) \leq 0$.

Remark

- Precise clinical identification of $\tilde{\theta}_i^H$ would have important clinical and allocative efficiency implications.
- Precise clinical identification of $\tilde{\theta}_i^H$ opens the possibility of a theranostic approach to precision medicine [3].

[2](Culyer & Wagstaff, 1993)
[3](Wong, 2015)

Patient's optimal level of care

The child's optimal quantity of care:

$$y_i^* = h_i(\tilde{\theta}_i^H) + \tilde{\theta}_i^H. \tag{2}$$

A child's need-based quantity of care is determined by:

- their severity of exposure, which is captured by the health status marker $h_i(\tilde{\theta}_i^H)$ and
- their innate unobserved ability to recover, which is captured by their pre-exposure health stock, $\tilde{\theta}_i^H$.

Physician treatment choice

The medical care team provides a quantity of care to maximize their perceived benefit $\tilde{\mathcal{U}}$ to the child:

$$\tilde{\mathcal{U}}(y_i|h_i,\tilde{\theta}_i^H) = \mathcal{U}(y_i|h_i,\tilde{\theta}_i^H) + \lambda_g(\tilde{\theta}_i^H)y_i, \tag{3}$$

where $\lambda_g(\tilde{\theta}_i^H) \in \mathbb{R}$ captures the regional differences in practice patterns.

- Differences in practice patterns is an active area of research[4].
- Draw on clinical investigation of equipoise to suggest uncertainty of an individual's health stock and clinical trajectory may influence group practice.
- Standard of care - physician training generally uniform.
- Standard of care - health delivery generally uniform.

[4](Chandra & Staiger, 2017)

Institutional constraints

Given institutional constraints, the medical care team chooses a quantity of care:

$$y_i^* = argmax_y \tilde{\mathcal{U}}(y_i|h_i, \tilde{\theta}_i^H) - C_g y_i, \tag{4}$$

where $C_g \in \mathbb{R}$ reflects their regional institutional setting and constraints.

- Direct financial constraints.
- Patient flow: Uncertain arrivals and service times.
- Congestion.

Optimal quantity of care

The optimal quantity of care provided by the care team is,

$$y_i^* = h_i(\tilde{\theta}_i^H) + \tilde{\theta}_i^H + \lambda_g(\tilde{\theta}_i^H) - C_g, \tag{5}$$

- Theoretical basis for our main estimating equation.
- Primary focus is on the relationship between the response utilization y_i^* and the severity of exposure $h_i(\tilde{\theta}_i^H)$.

Remark

- An unmeasured $\tilde{\theta}_i^H$ would confound a proxy for $h_i(\tilde{\theta}_i^H)$ in an analysis of equilibrium y_i^*.

In current practice:

- Illness severity score serve as proxies for $h_i(\tilde{\theta}_i^H)$.
- $\tilde{\theta}_i^H$ is unobserved.

Illness severity scores as surrogate markers for $h_i(\tilde{\theta}_i^H)$

- Objective measure of the physiologic state of the patient.
- (i) Predict morbidity and mortality, (ii) assess quality of care, (iii) evaluate and guide complex systems of care, and (iv) ultimately improve patient outcomes.
- Contribute to *situational awareness* and widely used in many countries, including Canada.
- Pediatric Risk of Mortality Score (PRISM)[5].
- Pediatric Index of Mortality (PIM)[6].

[5](Pollack et al, 2016)
[6](Straney et al, 2013)

Pediatric Risk of Mortality Score (PRISM)[7]

- Cardiovascular (heart rate, systolic blood pressure, and temperature),
- Neurologic (pupillary reactivity and mental status),
- Respiratory (arterial Po_2, pH, Pco_2, and total bicarbonate),
- Chemical (glucose, potassium, blood urea nitrogen, and creatinine),
- Hematologic (WBC count, platelet count, prothombin, and partial thromboplastin time).

[7](Pollack et al, 2016)

Pediatric Index of Mortality (PIM)[8]

- Physiology (systolic blood pressure, base excess,and Pao_2) ,
- Neurologic status (pupillary reaction)
- Mechanical ventilation,
- Admission type (elective, postoperative, postoperative-cardiac),
- Diagnosis (low or high risk).

[8](Straney et al, 2013)

y^*: Health utilization in the PICU -Durations

- PICU length of stay (LoS) is the primary measure of economic utilization in the intensive care environment.
- Durations of use are the primary measure of clinical utilization in the PICU environment:
- Duration of mechanical ventilation.
- Duration of ECLS/ECMO.
- Time on vasopressors.
- Time on nitric oxide.

Econometric model and issues

Move from theoretical model to econometric model:

$$y_i^* = h_i(\tilde{\theta}_i^H) + \tilde{\theta}_i^H + \lambda_g(\tilde{\theta}_i^H) - C_g, \tag{6}$$

- **Research task** $\Rightarrow$ Model health utilization y_i^* (duration) as a function of illness severity, proxy for $h_i(\tilde{\theta}_i^H)$.
- **Duration model of health utilization** $\Rightarrow$ Accelerated failure time (AFT).
- **Issues** $\Rightarrow$ Unmeasured confounding $\Leftarrow \tilde{\theta}_i^H$.
- **Methods** $\Rightarrow$ Robust instrumental variables (IV).

Accelerated life model

Underlying assumption is covariates "accelerate" or "decelerate" observed time, by a constant factor, $exp(s\beta + X_1\delta)$. Expressed as a transformation model:

$$y = s\beta + X_1\delta + \epsilon. \tag{7}$$

- $y \equiv ln(t)$: transformed $(n \times 1)$ durations,
- s : confounded observed $(n \times 1)$ risk scores,
- X_1 : observed $(n \times k_1)$ covariates, including confounded *Hospital* effect.
- ϵ : unobserved $(n \times 1)$ random disturbance, which includes an additive frailty term for $\tilde{\theta}_i^H$.

Also observe other $(n \times 1)$ instrumental variables Z: *Trauma* $(0 \leq \mathbb{P}(a_i = 1) \leq 1)$.

Assumptions

- Assumption **A 1**: X_1, Z predetermined, or
- Assumption **A 2**: Z, ϵ pairwise independent.
- Assumption **A 3**: (X_1, ϵ) independently distributed.

- Assumption **D 1**: ϵ distribution unspecified.
- Assumption **D 2,3,4**: $\epsilon \overset{iid}{\sim} Normal(0,1)$, Logistic(0,1) or Gumbel(0,1).

- No assumption on DGP linking s and Z or on the functional form of the first stage regression.

Rank inference

Rank inference strategy based on testing,

$$H_o : \beta = \beta_0, \quad H_1 : \beta \neq \beta_0, \tag{8}$$

in model (7), which implies testing $H_o : \gamma = 0$ in the transformed regression,

$$W = Z\gamma + \mu, \tag{9}$$

where,

$$W = y - s\beta_o - X_1\hat{\delta}(\beta_o), \tag{10}$$

is the aligned residual about the hypothesized β, where $\hat{\delta} = (X'X)^{-1}X'(y - s\beta_o)$ is the null restricted least squares estimator of δ.

Aligned linear rank statistic.[9]

- Generalize Andrews & Marmer (2008) test statistic for $H_o : \beta = \beta_o \Rightarrow \gamma = 0$:

$$rank(y - s\beta_o - X_1\hat{\delta}(\beta_o)) = Z\gamma + \mu, \tag{11}$$

- Test statistic:

$$GAM(\beta_o) = c(i)'\,(p_z)\,c(i), \tag{12}$$

where: $(n \times n)$ matrix $p_z = z(z'z)^{-1}z'$

- c is a score vector of: $(i) = rank(y - Y\beta_o - x_1\hat{\delta})$.
- n-column vector, $c : [0, 1) \to \mathbb{R}$ is the rank preserving non stochastic score.

[9] (Andrews & Marmer, 2008)

Exact null distribution.

For each draw j, where the $(n \times 1)$ vector $\mathbf{u}_j$ is drawn from the uniform [0,1] distribution, we have the jth realization of the GAM statistic:

$$\overline{GAM}_j = c(rank(u_j))' (p_z)\, c(rank(u_j)) \Rightarrow gam_{calc}(\alpha), \qquad (13)$$

- Repeat for j=1..J.
- Construct the simulated exact null distribution.
- Appropriate α-level cut off value, $gam_{calc}(\alpha)$ may subsequently be utilized in the confidence set construction.
- Distribution free.

Confidence set construction.

To construct a confidence set on β_o, we invert (12) using the appropriate α-level cut off:

$$C_\beta(\alpha) = [\beta_o : GAM(\beta_o) < gam_{calc}(\alpha)], \tag{14}$$

Solution permits sets that are *closed, open, empty, or the union of two or more disjoint intervals.*[10]

[10](Dufour, 1997)

Rank scores.

- Rank scores are derived to be efficient for certain distributional specifications, F_o.
- However, they are robust to misspecification.[11].
- The score vector satisfy a non-decreasing and non-constant condition, $c^{(i)} \leq ... \leq c^{(n)}$ and $c^{(i)} \neq c^{(n)}$, where (i) is the rank label of the associated aligned residual order statistic.
- Two related and asymptotically equivalent scores are the quantile F_o scores and the expected value F_o scores.

[11](Chernoff & Savage, 1958)

Rank scores: Quantile and expected value.[12]

- Quantile F_o scores:

$$c^{(i)} = F_o^{-1}\left(\frac{(i)}{(n+1)}\right). \tag{15}$$

- Expected value F_o scores:

$$c^{*(i)} = E_{F_o}[V^{(i)}], \tag{16}$$

where $V^{(i)}$ is the ith order statistic in a random sample of size n and (i) is the rank label of the associated aligned residual order statistic.

[12](Randles & Wolfe, 1979)

Clinical analysis

Research Question $\Rightarrow$ What is the relationship between a patient's length of stay (LoS) in the pediatric intensive care unit (PICU) and their illness severity score at the time of admission?

- **Outcome** $\Rightarrow$ Pediatric intensive care unit length of stay (LoS_i) measured in hours.
- **Exposure** $\Rightarrow$ Illness severity index as a marker of the exposure, as measured by either PIM_i and $PRISM_i$.
- **Data** $\Rightarrow$ Prospectively collected observational data set. Six centres and $i = 1...10,044$ patients over a two year period representing 1,184,726 PICU hours.

Complications

Primary complication $\Rightarrow$ Unmeasured factors may affect both exposure (illness severity) and outcome (LoS). Since randomized control study design may not be feasible, the use of instrumental variables provides one possible solution to this problem.

Secondary complication $\Rightarrow$

- Long stay (>10 days) (1,078/10,044) 12 % of sample used (663,368/1,184,726hrs) 56 % of PICU hours.
- Trauma (658/10,044) 6.6 % of sample used (69,869/1,184,726hrs) 5.9 % of PICU hours.

Clinical Model and Trauma

$$ln(LoS_i) = \delta_H Hsp_{ig} + \beta Severity_i + \delta_A Agecat_i + \delta_N NChrndx_i + \delta_P Previcu_i + \delta_C Cardiac_i + \epsilon_i, \quad (17)$$

- Where the illness $Severity_i$ index PIM_i or $PRISM_i$ is confounded.
- Instrumental variables are a possible solution $\Longrightarrow Trauma_i$
- Our suggested instrument was based on the intuition that a patient that suffered a trauma was accidental. $(0 \leq \mathbb{P}(a_i = 1) \leq 1)$
- Assignment mechanism was not a function of latent health stock. $Trauma_i$ only influenced health utilization through severity of exposure: $Severity_i$.

Results: 95% Confidence intervals

Distribution	Method	PRISM	PIM
Log-normal	AFT Likelihood	(0·065, 0·073)	(0·246, 0·274)
Log-logistic		(0·074, 0·081)	(0·273, 0·301)
Weibull		(0·071, 0·080)	(0·321, 0·356)
Log-normal	AFT- Gamma Frailty - Likelihood	(0·061, 0·068)	(0·218, 0·246)
Log-logistic		(0·072, 0·080)	(0·261, 0·289)
Weibull		(0·068, 0·075)	(0·241, 0·270)
Log-normal	Anderson-Rubin	(0·089, 0·262)	(0·071, 0·189)
Log-logistic	Generalized	(0·091, 0·257)	(0·073, 0·187)
Weibull		(0·090, 0·261)	(0·071, 0·188)
Weibull	Rank quantile scores	(0·145, 0·374)	(0·090, 0·215)

Precision medicine: $h_i(\tilde{\theta}_i^H)$ and $\tilde{\theta}_i^H$

Clinical implementation of gene-expression based markers for PICU septic shock patients[13].

- Pediatric Sepsis Biomarker Risk Model (PERSEVERE): panel of serum protein biomarkers to proxy $h_i(\tilde{\theta}_i^H)$.
- Gene-expression technology identifying 100 genes reflecting adaptive immunity and glucocorticoid receptor signalling.
- Endotyping to proxy $\tilde{\theta}_i^H$.
- Gene-expression score to proxy $\tilde{\theta}_i^H$.

[13](Wong et al 2015)

Endotypes and Illness severity scores

- Prospective validation of septic shock endotypes.
- Observationally similar PRISM scores for endotype A and B.
- However, very different clinical course - health utilization - 'complicated course'.
- Different clinical outcomes and response to adjunctive therapies.

Precision medicine in the PICU

Motivation & Challenges

- Heterogenous syndromes rather than disease specific.
- Rapidly changing health trajectories.
- High risk therapies with unclear therapeutic efficacy.

Objective

- Model endotype transition during acute phase of septic shock.
- Working towards a theranostic approach to septic shock.

Conclusion

- Clinically relevant question with useful economic implications.
- Provided a theoretical model to motivate econometric analysis.
- Proposed a novel method of robust inference in duration analysis.
- Extended the identification robust instrumental variables approach to duration analysis.
- Validating a framework for future precision medicine initiatives in the PICU.
- Our analysis reveals that direct use of currently available illness severity measures likely mask the attributable effect of health status on health utilization.

References

Anderson, T. W. & Rubin, H. (1949).
Estimation of the parameters of a single equation in a complete system of stochastic equations.
The Annals of Mathematical Statistics **20(1)**, 46–63.

Andrews, D. W. K. & Marmer, V. (2008).
Exactly distribution free inference in instrumental variables regression with possibly weak instruments.
Journal of Econometrics **142**, 183–200.

Chandra, A. & Staiger, O. (2017).
Identifying sources of inefficiency in health care.
National Bureau of Economic Research, Working paper **24035**.


Chernoff, H. & Savage, I. R. (1958).
Asymptotic normality and efficiency of certain non-parametric test statistics.
The Annals of Mathematical Statistics **29**, 972–994.


Culyer, C. J. & Wagstaff, A. (1993).
Equity and equality in health and health care.
Journal of Health Economics, **12(4)**, 431–457.


Dufour, J. M. (1997).
Some impossibility theorems in econometrics with applications to structural and dynamic models.
Econometrica **65**, 1365–1387.

Finkelstein, A. Gentzkow, M. & Williams, H. (2016).

Sources of geographic variation in health care: evidence from patient migration.
Quarterly Journal of Economics **131**, 1681–1726.

Pollack, M. M., et al (2016).
The Pediatric Risk of Mortality Score: Update 2015.
Pediatric Critical Care Medicine **17:1**, 2–9.

Pollack, M. M., Patel, K. & Ruttimann, U. E. (1996).
PRISM III: An updated Pediatric Risk of Mortality score.
Critical Care Medicine **24**, 743–752.


Randles, R. H. & Wolfe, D. A. (1979).
Introduction to the Theory of Nonparametric Statistics.
John Wiley & Sons.


Slater, A., Shan, F. & Pearson, G. (2003).
PIM2: A revised version of the paediatric index of mortality.
Intensive Care Medicine **29**, 278–285.


Straney, l., et al (2015).
Paediatric Index of Mortality 3: An Updated Model for Predicting Mortality in Pediatric Intensive Care.
Pediatric Critical Care Medicine **14:7**, 673–681.


Wong, H. R. et al (2015).
Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock.
Am J Respir Crit Care Med **191:3**, 309–315.