Protective Effects of Rheumatoid Arthritis in Septic ICU Patients

Mallory Sheth, Abdullah Chahin, Roger Mark, Natasha Markuzon

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Sepsis and Immune Modulation

- Sepsis is a systemic inflammatory response to an infection that can lead to organ failure and death
- The role of immune modulation in sepsis is not entirely understood
  - Some research suggests that pro-inflammatory cytokine release is largely responsible for the collateral damage inflected by the immune response on the host tissues
  - Other research suggests that patients are more likely to die from opportunistic infections than from hyperinflammation
- What factors impact mortality in severe sepsis?

Comorbidities Impact Sepsis Survival

- We analyzed the MIMIC II database for 2001-2008 to identify sepsis subgroups with atypical 30-day mortality
- Different comorbidities have different mortality rates

Group	30-Day Mortality
All Sepsis	**50.1%**
Sepsis + Lymphoma	76.3% **(+ 26.2)**
Sepsis + Metastatic Cancer	67.7% **(+ 17.6)**
Sepsis + RA	29.0% **(- 21.1)**

Key Observation: Septic patients with rheumatoid arthritis (RA) have significantly lower observed mortality rates

Identifying Patients with Sepsis

Sepsis Definition	N	30-Day Mortality
(1) ICD-9-CM code for infection and organ dysfunction (Angus)	6,661	32.7%
(2) ICD-9-CM code 038 for septicemia	2,876	40.7%
(3) ICD-9-CM code 038 for septicemia and hypotension	1,302	50.1%

- There are different ways to identify sepsis patients
  - Definition (1) (Angus) captures the most patients but may overestimate the incidence of severe sepsis
  - Definition (2) (Septicemia) selects a smaller, more targeted population

Identifying Patients with Sepsis

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- This study primarily uses Definition (3) (Septicemia and Hypotension)
  - Definition (3) is the most selective criteria with the highest likelihood of true sepsis

RA is Protective in Severe Sepsis

- The death rate for septic patients (def. 3) with RA is 29%, **21 percentage points lower** than sepsis overall
- This result holds generally for septic patients with auto-immune disorders.
  - Includes RA, SLE, ulcerative colitis, MS, etc.

Group	30-Day Mortality
All Sepsis (N=1,302)	**50%**
Sepsis + RA (N=31)	29%
Sepsis + Auto-Immune Disorders (N=65)	29%

What Could Explain the Apparent Protective Effect?

- Patient severity or other demographic information
  - But difference in mortality is significant after controlling for gender, age, and SOFA
- Patient drug regimens
  - Corticosteroids are anti-inflammatory drugs, so is the medication itself protective as opposed to RA?
    - Patients with RA are 8x more likely to use prednisone at home and more likely to receive steroids in the hospital.
- Study inclusion criteria

Corticosteroid Use Does Not Explain Protective Effect

- Difference in mortality is still significant after controlling for use of corticosteroids
  - Mortality rates are 20 percentage points lower for septic patients with RA, regardless of steroid use

Treatment	RA		No RA	
	#	Death Rate	#	Death Rate
Home Prednisone	11	27.3%	54	48.1%
No Home Prednisone	20	30.0%	1,212	50.6%

Importance of Sepsis Severity

- Septic patients with RA have lowered 30-day mortality regardless of sepsis definition
  - 3 pct point difference for least severe cohort
  - 8 pct point difference for middle cohort
- But observed effect is only significant for most critically ill patients

Outcome: 30-Day Mortality

Sepsis Definition	Severity	RA	No RA	Sig?
Definition (1) Angus	Lowest	30%	33%	X
Definition (2) Septicemia (038)	Middle	32%	40%	X
Definition (3) 038 + Hypotension	Highest	31%	52%	√

Importance of ICU Length of Stay

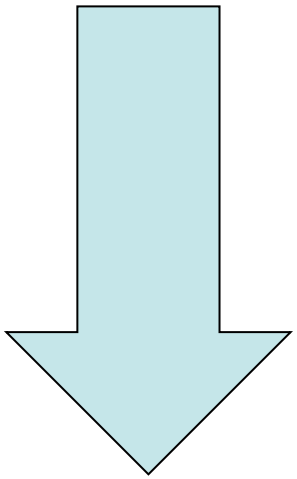
- Protective effect is significant for patients with at least 24 hours in the ICU
  - Effect is even stronger for patients with a stay of 72+ hours; confirms more severe patients benefit most from RA
- Protective effect is dampened for sepsis patients who stay less than one day
  - Difference in 30-day mortality shrinks from 21 to 14 percentage points

Conclusions

- RA and other auto-immune disorders provide a survival benefit in severe sepsis
  - Lowered mortality is significant, even after controlling for demographics, patient severity, and steroid use
  - Suggests that protective effect is broadly related to immune modulation in sepsis
- The effect is strong for patients with severe sepsis and at least 24 hours in the ICU
  - Suggests a “sweet spot” for patient severity
    - Protective effect is not significant for less severe sepsis patients and patients discharged on first day
    - But patients who are too sick and die on first day also do not benefit

Conclusions: Role of Big Data

- We have clinical data for over 30,000 adult ICU stays, but only 31 severe sepsis patients with RA
  - Big data gives us the ability to study rare events and identify subgroups where effects are strong



2,876 (sepsis)

1,302 (severe sepsis)

31 (rheumatoid arthritis)

Will the results hold for larger samples & other datasets?

Other Questions for Future Analysis

- Do disease-modifying anti-rheumatic drugs (DMARDs) explain the observed survival benefit?

- Is the rate of organ failure different for severe sepsis patients with auto-immune disease?

The Team

Mallory Sheth
Massachusetts Institute of Technology
Operations Research Center

Dr. Natasha Markuzon, Ph.D
The Charles Stark Draper Laboratory, Inc.

Dr. Abdullah Chahin, M.D.
Beth Israel Deaconess Medical Center

Dr. Roger G. Mark, M.D. Ph.D
Massachusetts Institute of Technology
Laboratory for Computational Physiology

Questions?

Appendix: Characteristics of Septic Patients

	RA	No RA	p-value
N	**31**	**1,271**	--
Mortality			
30-day	29.0%	50.6%	0.016
Patient Characteristics			
Gender (% Male)	41.9%	55.5%	0.130
Age (Mean ± SE)	65.1 ± 2.7	67.7 ± 0.5	0.358
SOFA (Mean ± SE)	10.1 ± 0.9	10.1 ± 0.1	0.978

- On average, RA patients are younger and more likely to be female.
- Difference in mortality is still significant after controlling for age, gender, and SOFA

Appendix: Other Auto-Immune Disorders

Condition	N	Death Rate
All Severe Sepsis	**1,302**	**50%**
All Auto-Immune	**65**	**29%**
rheumatoid arthritis	15	27%
ulcerative colitis	15	33%
Crohns disease	13	46%
multiple sclerosis	12	25%
systemic lupus erythematosus	8	13%
myasthenia gravis	4	0%
ankylosing spondylitis	1	0%
psoriatic arthritis	0	--

- Suggests that protective effect is broadly related to immune modulation in sepsis

Appendix: Corticosteroid Use for Septic Patients

	RA	No RA	p-value
N	**31**	**1,271**	--
Treatment (Home)			
Home Prednisone	35.5%	4.3%	0.000
Treatment (Hospital)			
Any Steroids	64.5%	37.7%	0.002
Prednisone	54.8%	14.7%	0.000
Hydrocortisone	51.6%	30.8%	0.012

- Patients with RA are eight times more likely to use prednisone at home and more likely to receive steroids in the hospital.
- Use of corticosteroids does not explain the observed protective effect

Appendix: Results for Different Inclusion Criteria

Outcome: 30-Day Mortality

Sepsis and Hypotension Definition	RA	No RA	p-value (χ^2)	p-value (logistic)
Angus	30%	33%	0.39	0.77
038, No Hypotension Required	32%	40%	0.12	0.21
038 + Hypotension + Angus	31%	52%	0.03	0.03
038, 3 MAP <= 65 (20 Min)	28%	54%	0.01	0.01
038, 3 MAP <= 65 (60 Min)	31%	49%	0.02	0.04
038, Vasopressors	32%	48%	0.03	0.04

- A certain level of sepsis severity is required to observe a significant protective effect
- Results are robust to different definitions of hypotension.