Nephrology and Transplantation Department
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AKI in COVID-19

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Labbafinejad Medical Center,SBMU

October 1th, 2021

AKI in Covid-19 Patients
What is New?

Lui G Forni

Consultant Intensivist & Nephrologist

58TH ERA-EDTA CONGRESS
FULLY VIRTUAL
JUNE 5-8, 2021

NHS

GIRFT
GETTING IT RIGHT FIRST TIME

December 2020

Clinical practice guide for improving the management of adult COVID-19 patients in secondary care

Shared learning from high performing trusts during COVID-19 pandemic

ABCD
Association of British Clinical Diabetologists

BGS
British Geriatrics Society
improving healthcare for older people

British Thoracic Society

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DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

Faculty of Intensive Care Medicine

intensive care society 50

RCoA
Royal College of Anaesthetists

The Royal College of Emergency Medicine

The Royal College of Pathologists
Pathology: the science behind the cure

Royal College of Physicians

Royal College of Surgeons of England

sam
THE SOCIETY FOR ACUTE MEDICINE

Renal support

- Continuous renal replacement therapy (CRRT) and fluids had significant supply issues in the first wave. Mutual aid from trust renal services and more innovative solutions should be considered if this recurs. It should be recognised that renal support for those patients outside of a CC setting should be undertaken in centres that are capable and experienced in delivering dialysis services.
- *London North West University Healthcare NHS Trust's* critical care unit worked with their renal service to meet CRRT demand through use of mobile dialysis machines, traditionally used in the home setting. (2)
- *Guys and St Thomas' NHS Foundation Trust* utilised resources in house to aseptically produce equivalent fluid used for CRRT when external supplies of dialysis fluid were not available. However, this would only be feasible for relatively small volumes and would need to be undertaken with the support of pharmacy colleagues.

Patient-Oriented, Translational Research: Research Article

American Journal of Nephrology

Am J Nephrol
DOI: 10.1159/000507471

Received: March 11, 2020
Accepted: March 24, 2020
Published online: March 31, 2020

Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China

Luwen Wang[a] Xun Li[a] Hui Chen[c] Shaonan Yan[a] Dong Li[b] Yan Li[b]
Zuojiong Gong[a]

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icnarc | intensive care national audit & research centre

25 years and counting...

Napier House
24 High Holborn
London WC1V 6AZ
email: COVID-19@icnarc.org
www.icnarc.org

ICNARC report on COVID-19 in critical care:

England, Wales and Northern Ireland

10 May 2021

Table 24. Critical care outcome by patient characteristics, admitted up to 30 March 2021

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Patient subgroup	Patients with confirmed COVID-19 and outcome received (N=24,961)	
	Discharged alive from critical care n (%)	Died in critical care n (%)
Any very severe comorbidities *		
No	14198 (62.8)	8426 (37.2)
Yes	922 (46.9)	1044 (53.1)
Any respiratory support *		
Basic only	8725 (82.4)	1859 (17.6)
Advanced	6013 (43.8)	7717 (56.2)
Any renal support *	1244 (30.4)	2850 (69.6)

This is need for RRT not AKI rates

Original research

Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis

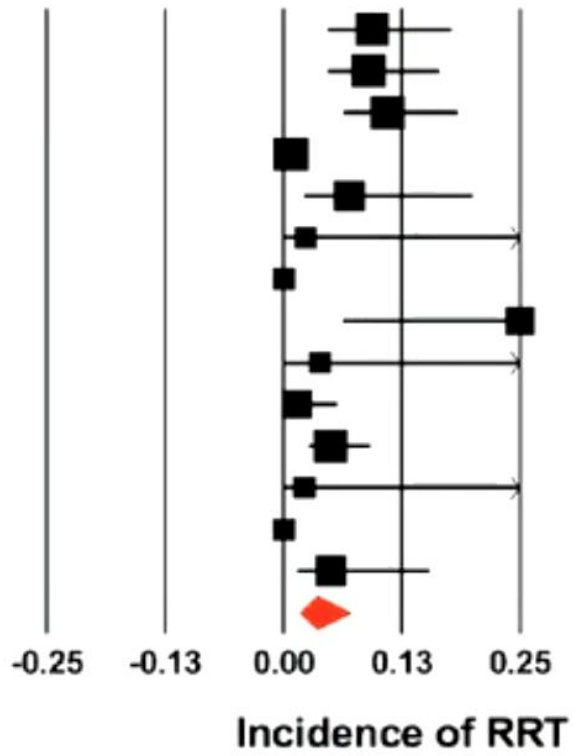
Panupong Hansrivijit ,[1] Chenchen Qian,[1] Boonphiphop Boonpheng,[2] Charat Thongprayoon ,[3] Saraschandra Vallabhajosyula,[4] Wisit Cheungpasitporn,[5] Nasrollah Ghahramani[6]

BMJ

Hansrivijit P, *et al*. *J Investig Med* 2020;**68**:1261–1270. doi:10.1136/jim-2020-001407

Incidence of RRT

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Du Y, 2020	0.094	0.048	0.177	-6.096	0.000
Chen, 2020	0.090	0.047	0.164	-6.588	0.000
Du, 2020	0.110	0.064	0.184	-6.830	0.000
Guan, 2020	0.008	0.004	0.015	-14.235	0.000
Huang, 2020	0.070	0.022	0.200	-4.226	0.000
Lei, 2020	0.024	0.001	0.287	-2.594	0.009
Lian, 2020	0.001	0.000	0.010	-5.205	0.000
Ling, 2020	0.250	0.063	0.623	-1.346	0.178
Liu Y, 2020	0.038	0.002	0.403	-2.232	0.026
Wang, 2020	0.015	0.004	0.056	-5.925	0.000
Zhou, 2020	0.050	0.027	0.092	-8.869	0.000
Arentz, 2020	0.023	0.001	0.277	-2.629	0.009
Cheng KI, 2020	0.001	0.000	0.011	-5.122	0.000
Yang, 2020	0.050	0.015	0.155	-4.628	0.000
	0.036	0.018	0.071	-8.950	0.000



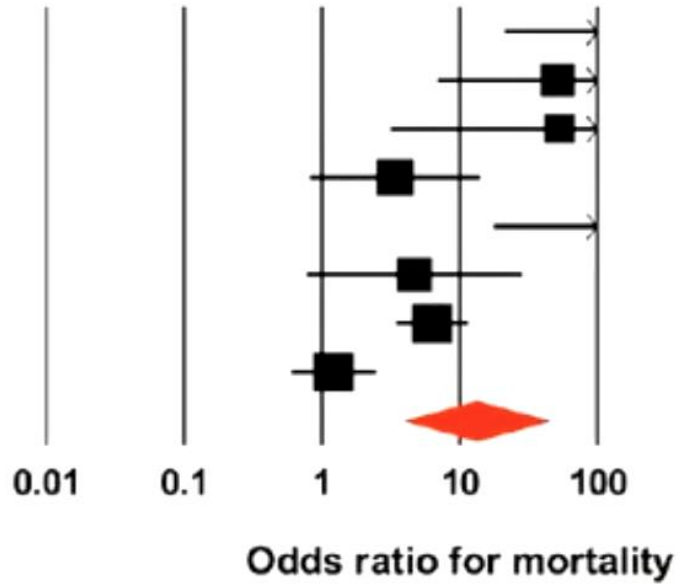
Hansrivijit P, *et al*. *J Investig Med* 2020;**68**:1261–1270. doi:10.1136/jim-2020-001407

Odds ratio for mortality from AKI

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cao J, 2020	120.000	21.273	676.925	5.424	0.000
Chen Tao, 2020	51.494	6.888	384.960	3.840	0.000
Ding, 2020	53.369	3.185	894.375	2.765	0.006
Yang, 2020	3.400	0.821	14.077	1.688	0.091
Zhou, 2020	136.000	17.716	1044.041	4.724	0.000
Du R, 2020	4.706	0.786	28.177	1.696	0.090
Cheng KI, 2020	6.340	3.471	11.582	6.007	0.000
Shi, 2020	1.220	0.598	2.490	0.546	0.585
	13.333	4.049	43.910	4.259	0.000

Statistics for each study

Odds ratio and 95% CI



Hansrivijit P, *et al*. *J Investig Med* 2020;**68**:1261–1270. doi:10.1136/jim-2020-001407

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Original Investigation

Kidney360

Characteristics, Outcomes and 60-Day Hospital Mortality of ICU Patients with COVID-19 and Acute Kidney Injury

Jyotsana Thakkar,[1] Sudham Chand,[2] Michael S. Aboodi,[2] Anirudh R. Gone,[1] Emad Alahiri,[1] David E. Schecter,[3] David Grand,[4] Deep Sharma,[1] Matthew K. Abramowitz,[1] Michael J. Ross,[1] Peter Dicpinigaitis,[2] and Sumit Kapoor[2]

KIDNEY360 1: 1339–1344, 2020. doi: https://doi.org/10.34067/KID.0004282020

Characteristics, outcomes and 60-day hospital mortality of patients with Covid-19 pneumonia and AKI in the intensive care unit (ICU)

Kidney360

Retrospective Observational

Montefiore
ICU admissions

March 10 to
April 11, 2020

COVID-19
pneumonia

n = 300

97% Required invasive mechanical ventilation for moderate-severe ARDS

74.6%
(n = 224)
Presented with or developed AKI subsequent to admission

50.45%
(n = 113)
AKI on Day 1 of ICU admission

Patients with AKI

50.8%
(n = 114)
Required Kidney Replacement Therapy (KRT)

70%
Mortality of patients requiring KRT

66.5%
60-day hospital mortality

Characteristics of in-hospital non-survivors at 60 days

- Older
- Higher admission and peak creatinine levels
- Higher admission hemoglobin
- Higher peak phosphate levels

Conclusions Covid-19 requiring ICU admission is associated with high incidence of severe AKI, necessitating KRT in approximately half of such patients. The majority of Covid-19 patients with AKI in ICU developed moderate to severe ARDS requiring invasive mechanical ventilation.

Jyotsana Thakkar, Sudham Chand, Michael S. Aboodi, et al. ***Characteristics, outcomes and 60-day hospital mortality of ICU patients with Covid-19 and acute kidney injury.*** *Kidney360*. doi: 10.34067/KID.0004282020.
Visual Abstract by Edgar Lerma, MD, FASN

CLINICAL RESEARCH www.jasn.org

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AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19

Shruti Gupta,[1] Steven G. Coca,[2] Lili Chan,[2] Michal L. Melamed,[3] Samantha K. Brenner,[4,5] Salim S. Hayek,[6] Anne Sutherland,[7] Sonika Puri,[8] Anand Srivastava,[9] Amanda Leonberg-Yoo,[10] Alexandre M. Shehata,[11] Jennifer E. Flythe,[12,13] Arash Rashidi,[14] Edward J. Schenck,[15] Nitender Goyal,[16] S. Susan Hedayati,[17] Rajany Dy,[18] Anip Bansal,[19] Ambarish Athavale,[20] H. Bryant Nguyen,[21] Anitha Vijayan,[22] David M. Charytan,[23] Carl E. Schulze,[24] Min J. Joo,[25] Allon N. Friedman,[26] Jingjing Zhang,[27] Marie Anne Sosa,[28] Eric Judd,[29] Juan Carlos Q. Velez,[30,31] Mary Mallappallil,[32] Roberta E. Redfern,[33] Amar D. Bansal,[34] Javier A. Neyra,[35] Kathleen D. Liu,[36] Amanda D. Renaghan,[37] Marta Christov,[38] Miklos Z. Molnar,[39] Shreyak Sharma,[1] Omer Kamal,[1] Jeffery Owusu Boateng,[40] Samuel A.P. Short,[41] Andrew J. Admon,[42] Meghan E. Sise,[43] Wei Wang,[44,45] Chirag R. Parikh,[46] David E. Leaf,[1] and the STOP-COVID Investigators*

Conclusions AKI-RRT is common among critically ill patients with COVID-19 and is associated with a hospital mortality rate of >60%. Among those who survive to discharge, one in three still depends on RRT at discharge, and one in six remains RRT dependent 60 days after ICU admission.

JASN 32: 161–176, 2021. doi: https://doi.org/10.1681/ASN.2020060897

AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

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METHODS

Multicenter cohort study

N = 3099 critically ill adults with COVID-19

Data from 67 hospitals across the United States

Logistic regression to identify risk factors for AKI-RRT

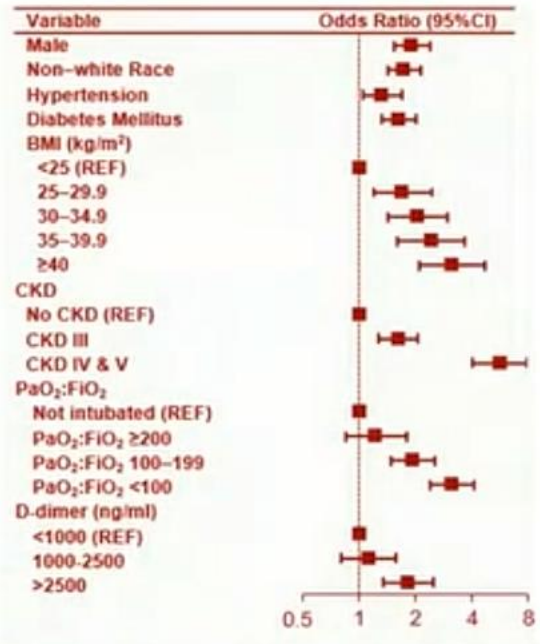
OUTCOME

21% of patients developed AKI-RRT

63% of AKI-RRT patients died in the hospital

34% of survivors remained RRT-dependent on discharge

Risk Factors for AKI-RRT

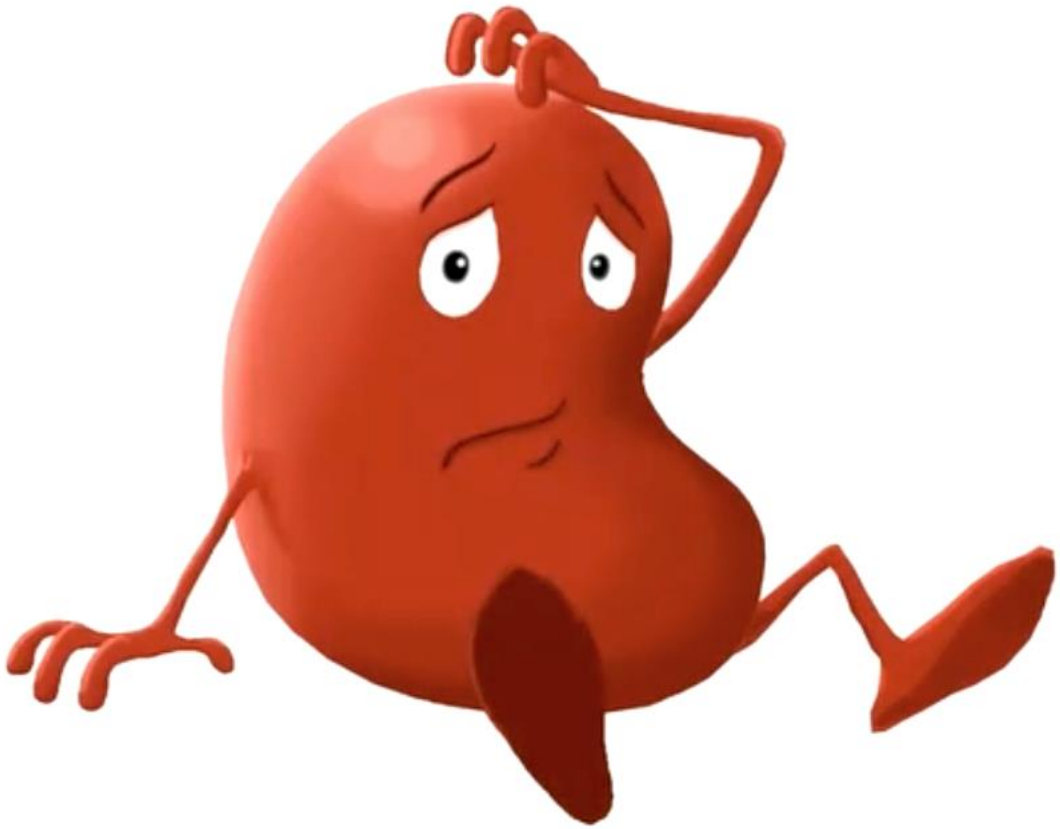


Conclusion

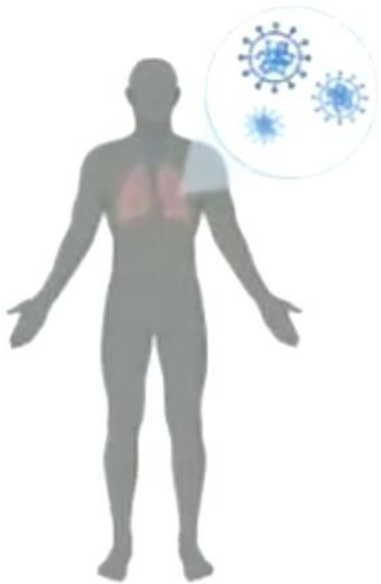
AKI-RRT is common in critically ill patients with COVID-19 and is associated with high inpatient mortality and persistent RRT dependence among survivors.

doi: 10.1681/ASN.2020060897

What's the Mechanism of Infection?



How Do Patients Get AKI?



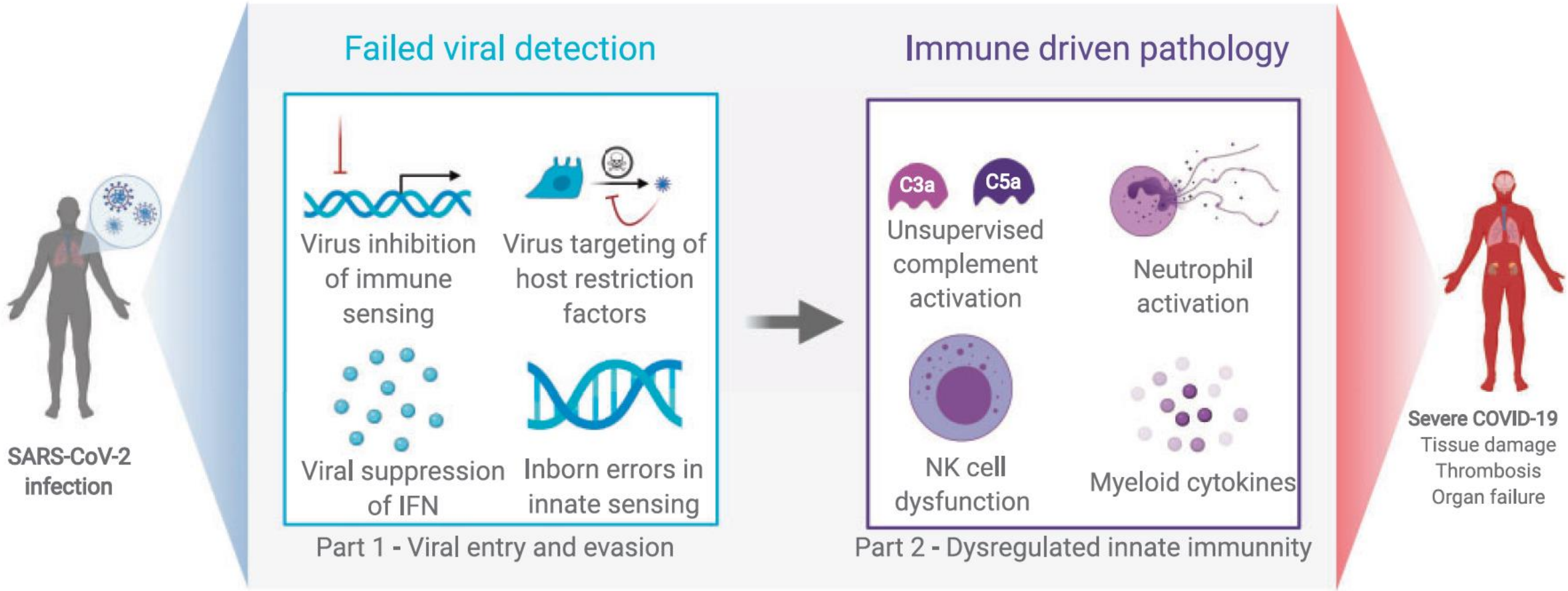
SARS-CoV-2 infection

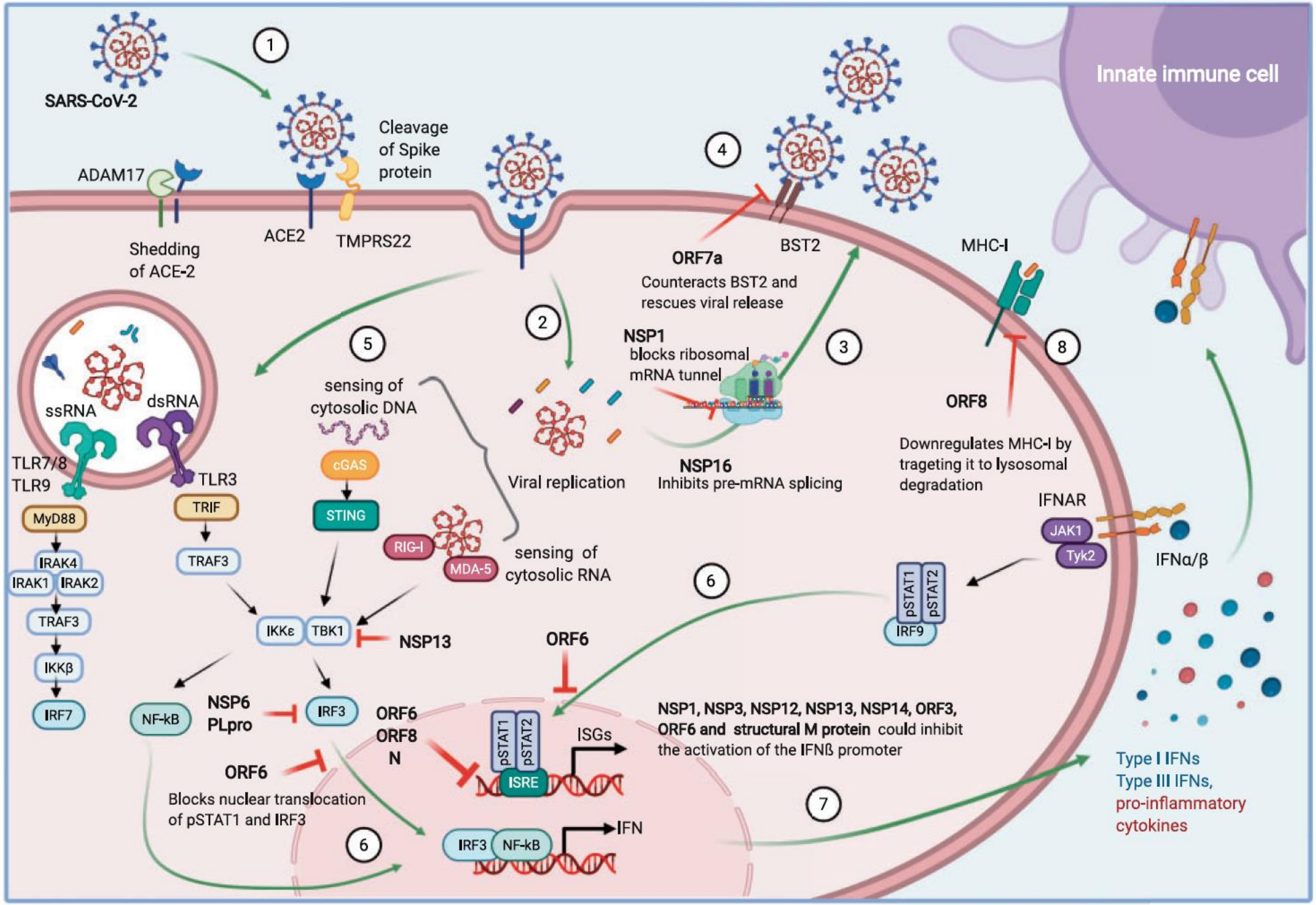
- Viral entry requires SARS-CoV-2 spike (S) glycoprotein binding to the ACE2 receptor
- Fusion of SARS-CoV-2 with the host cell requires transmembrane serine protease 2 (TMPRSS2) to cleave the Spike protein at the S1/S2 cleavage site
- S1 mediates receptor binding, whilst S2 is required for membrane fusion; both are needed for endocytosis into the host cell

Innate immunology in COVID-19 – A LIVING REVIEW PART I: Viral entry, sensing and evasion

*Clarissa Coveney[1], *Michel Tellier[2], *Fangfang Lu[1], *Shayda Maleki Toyserkani[1], Ruth Jones[1], Valentina M. T. Bart[1], Ellie Pring[1], Aljawharah Alrubayyi[1], Felix C. Richter[2], D. Oliver Scourfield[1], Jan Rehwinkel[2], Patricia R. S. Rodrigues[1], Luke C. Davies[1†], Ester Gea-Mallorquí[1†] and The Oxford-Cardiff COVID19 Literature Consortium.

Graphical Abstract




Innate immune cell
SARS-CoV-2
1
Cleavage of Spike protein
ADAM17
Shedding of ACE-2
ACE2
TMPRS22
4
ORF7a
Counteracts BST2 and rescues viral release
BST2
MHC-I
2
NSP1
blocks ribosomal mRNA tunnel
3
5
sensing of cytosolic DNA
ssRNA
dsRNA
TLR7/8
TLR9
TLR3
cGAS
STING
TRIF
MyD88
TRAF3
IRAK4
IRAK1
IRAK2
TRAF3
IKKβ
IRF7
RIG-I
MDA-5
sensing of cytosolic RNA
Viral replication
NSP16
Inhibits pre-mRNA splicing
8
ORF8
Downregulates MHC-I by trageting it to lysosomal degradation
IFNAR
JAK1
Tyk2
IFNα/β
IKKε
TBK1
NSP13
ORF6
6
pSTAT1
pSTAT2
IRF9
NF-kB
NSP6
PLpro
IRF3
ORF6
ORF8
N
ISGs
ISRE
NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6 and structural M protein could inhibit the activation of the IFNß promoter
ORF6
Blocks nuclear translocation of pSTAT1 and IRF3
6
IRF3
NF-kB
IFN
7
Type I IFNs
Type III IFNs,
pro-inflammatory cytokines

What's the Pathophysiology Behind AKI?

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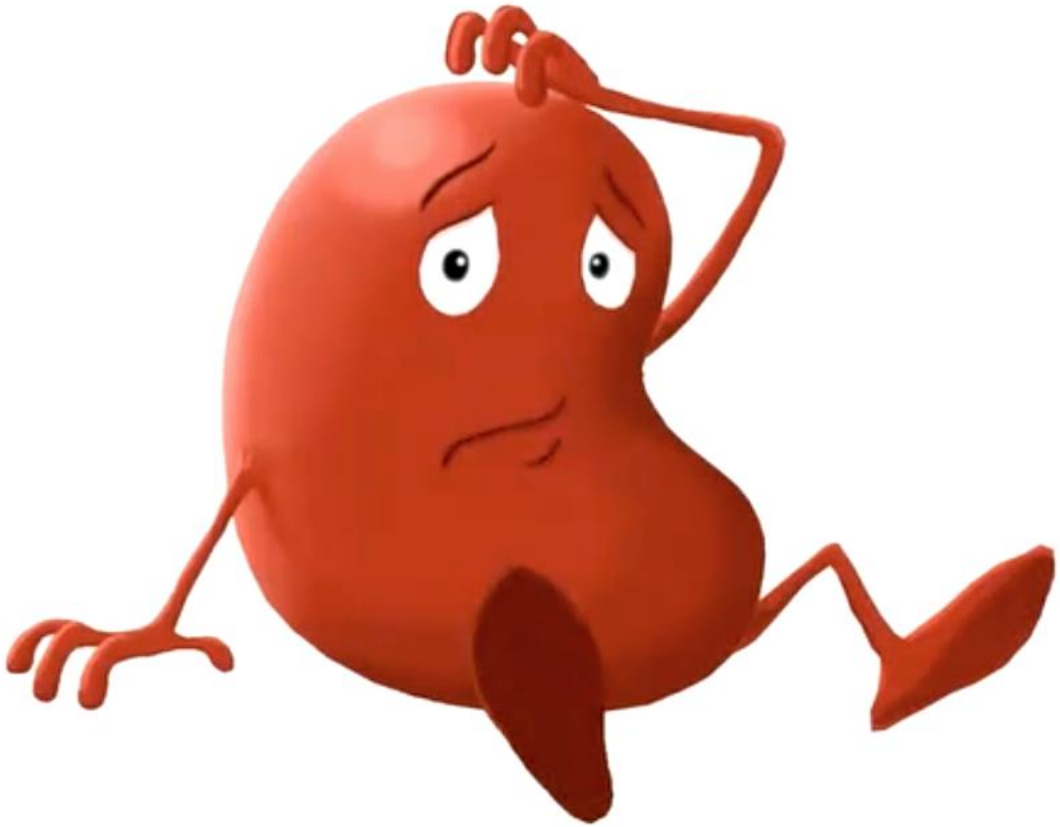


Is it all ARDS Related?

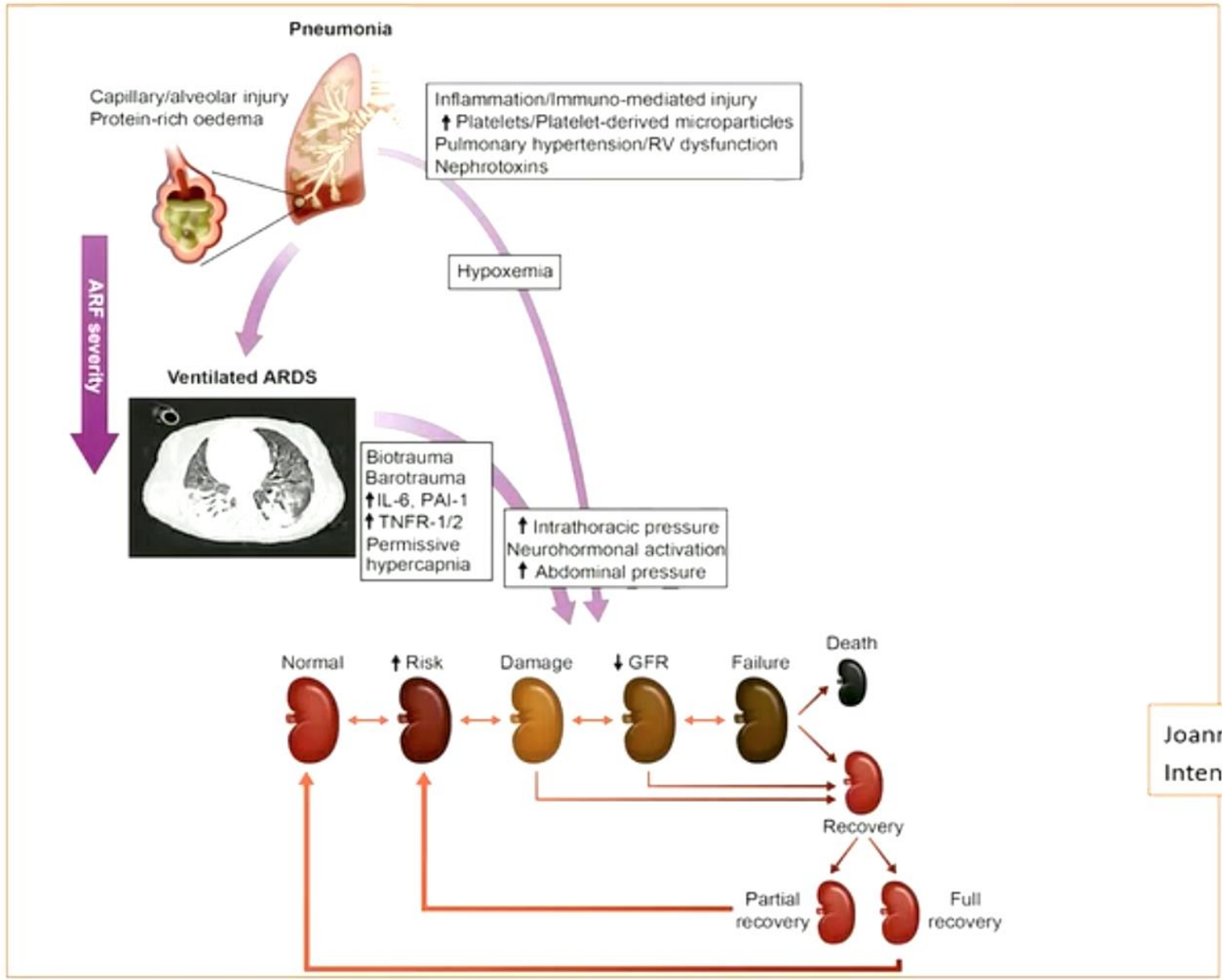
Mechanisms?

Intensive Care Med (2020) 46:654–672
https://doi.org/10.1007/s00134-019-05869-7

CONFERENCE REPORTS AND EXPERT PANEL

Lung–kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup

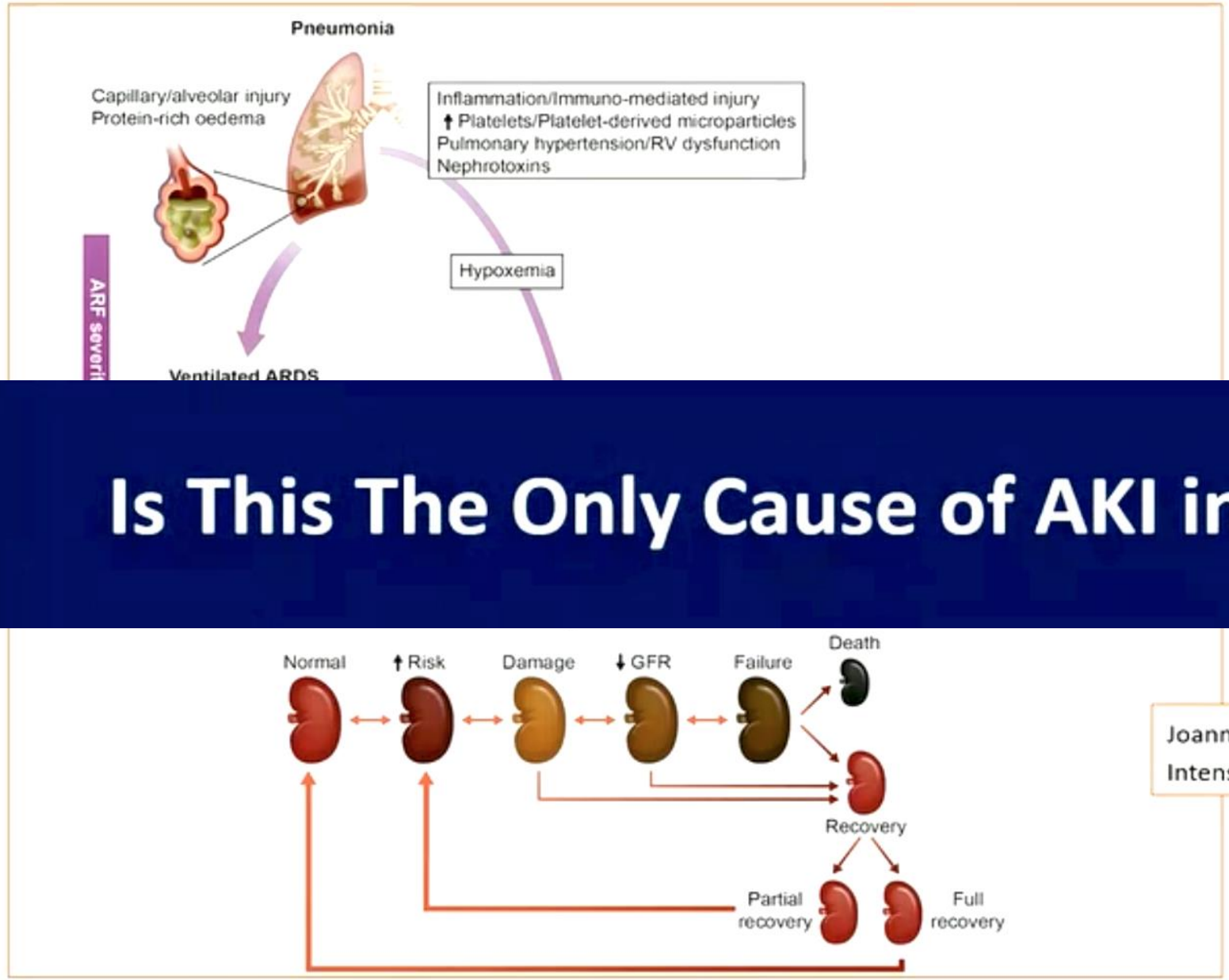
Michael Joannidis[1*], Lui G. Forni[2,3], Sebastian J. Klein[1,4], Patrick M. Honore[5], Kianoush Kashani[6], Marlies Ostermann[7], John Prowle[8,9], Sean M. Bagshaw[10], Vincenzo Cantaluppi[11], Michael Darmon[12,13,14], Xiaoqiang Ding[15], Valentin Fuhrmann[16,17], Eric Hoste[18,19], Faeq Husain-Syed[20], Matthias Lubnow[21], Marco Maggiorini[22], Melanie Meersch[23], Patrick T. Murray[24,25], Zaccaria Ricci[26], Kai Singbartl[27], Thomas Staudinger[28], Tobias Welte[29], Claudio Ronco[30,31,32] and John A. Kellum[33]



Joannidis et al ADQI 21
Intensive Care Med 2020

Table 2 Pathophysiological processes involved in lung–kidney interactions

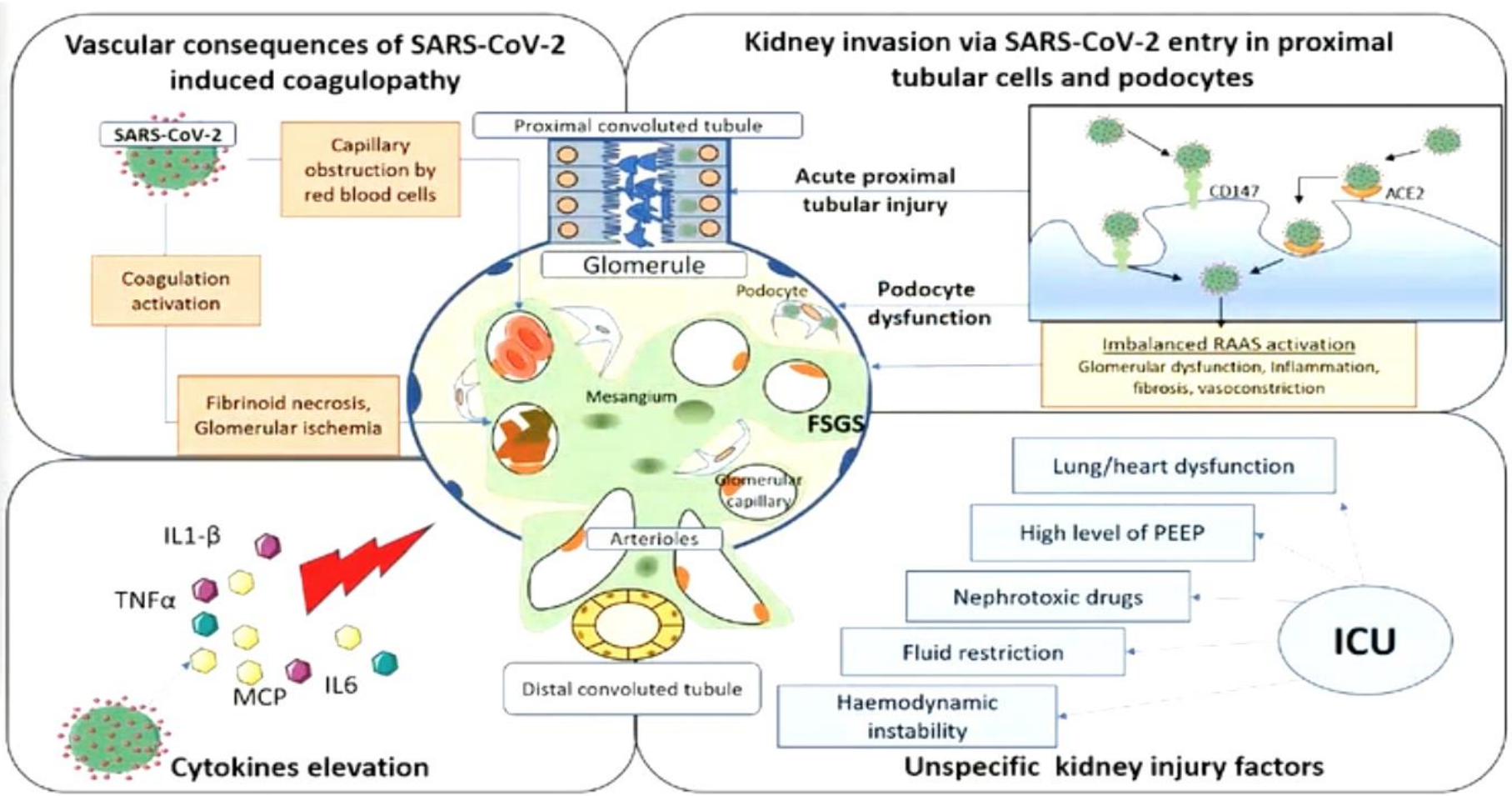
	Haemodynamic effects	Inflammatory/ immune- mediated effects	Effects of altered acid–base status	Effects of impaired gas exchange	Neuro-hormonal effects
Potential pathophysiological mechanisms	*Effects of acute pulmonary disease on kidney function*				
	Increased pulmonary arterial pressure leading to right ventricular failure with venous congestion [6, 57] Increased intra-abdominal pressure [77, 83] Increased intra-thoracic pressure [57, 64]	Increased release of pro-inflammatory mediators (IL-6, TNF-α, IL-1 beta, TGF-β, substance P) [16–19] Decreased release of anti-inflammatory mediators (IL-10)	Increased oxygen consumption in the proximal renal tubular system in respiratory acidosis [119]	*Hypercapnia* ($pCO_2 > 50$ *mmHg*): Loss of renal vasodilatory response, reduction of RBF and change in diuresis [46, 56] *Severe hypoxaemia* ($pO_2 < 40$ *mm Hg*): Reduction of RBF [45]	Activation of RAAS [65] Increased aldosterone secretion [65] Reduction of ANP/BNP levels [65] Activation of the sympathetic nervous system [65] Release of non-osmotic vasopressin [48]
	Additional effects of positive pressure ventilation on kidney function				
	Excessive increase in intrathoracic pressure leading to: reduced venous return [64] reduced left ventricular preload [64] reduced cardiac output [64] increased right ventricular afterload [57, 64] resulting in right ventricular dysfunction and venous congestion with increased renal back pressure [6, 57]	*Effect of injurious ventilation*: increased release of IL-6, PAI-1, TNFR-1 and TNFR-2 into systemic circulation [62] induction of renal epithelial cell apoptosis and dysregulation of extracellular ligands [63]	As above	*Permissive Hypercapnia:* as above *Hyperoxaemia:* lack of data	As above



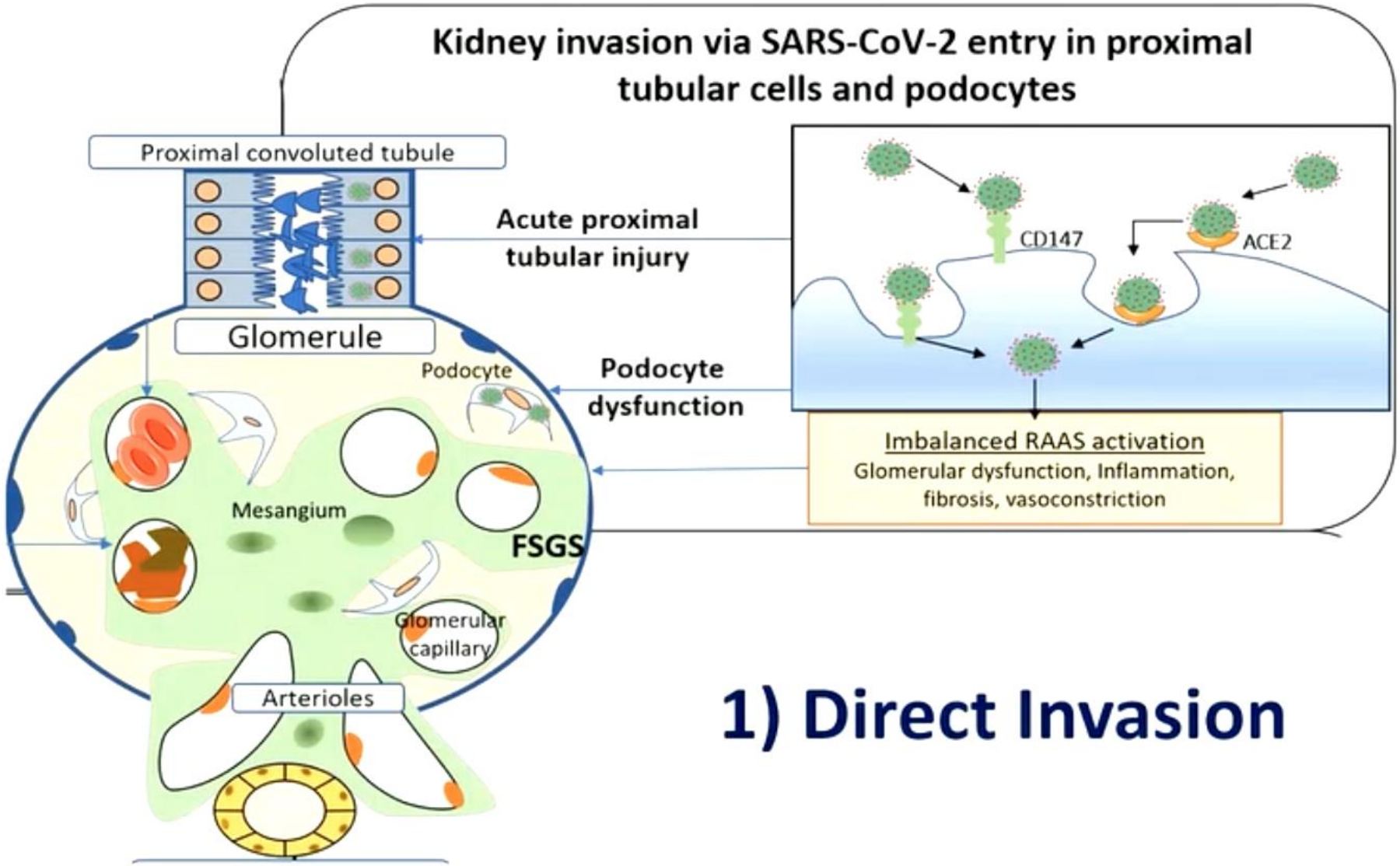
Is This The Only Cause of AKI in C-19?

Joannidis et al ADQI 21
Intensive Care Med 2020

Other Potential Mechanisms?



Intensive Care Med
https://doi.org/10.1007/s00134-020-06153-9



1) Direct Invasion

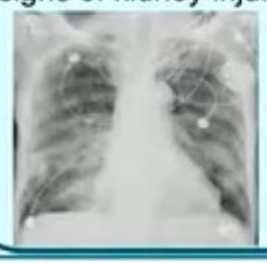
Mechanisms?

Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China

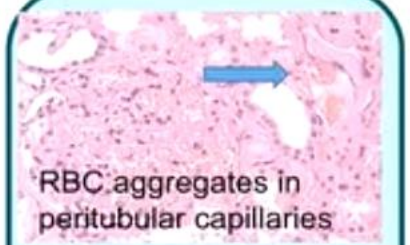
Study Cohort

26 autopsies in COVID-19 patients

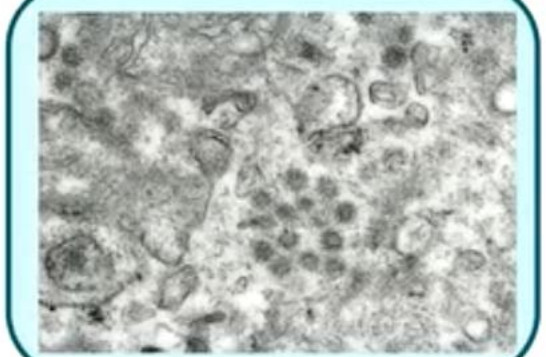
-death due to respiratory failure
-average age 69 years
-19 males; 7 females
-9/26 showed clinical signs of kidney injury



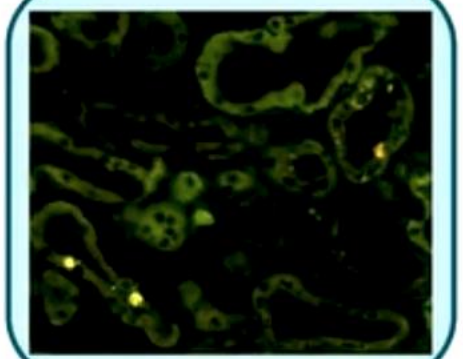
Light microscopy: ATI, RBC aggregates



Electron microscopy: virus in tubules and podocytes



SARS-CoV nuclear protein detection



CONCLUSION:
Direct parenchymal infection of tubular epithelial cells and podocytes with marked acute tubular injury (ATI) and erythrocyte aggregation occurs in severe lethal COVID-19.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Su et al, 2020

Evidence That C-19 Can Infect the Kidney?

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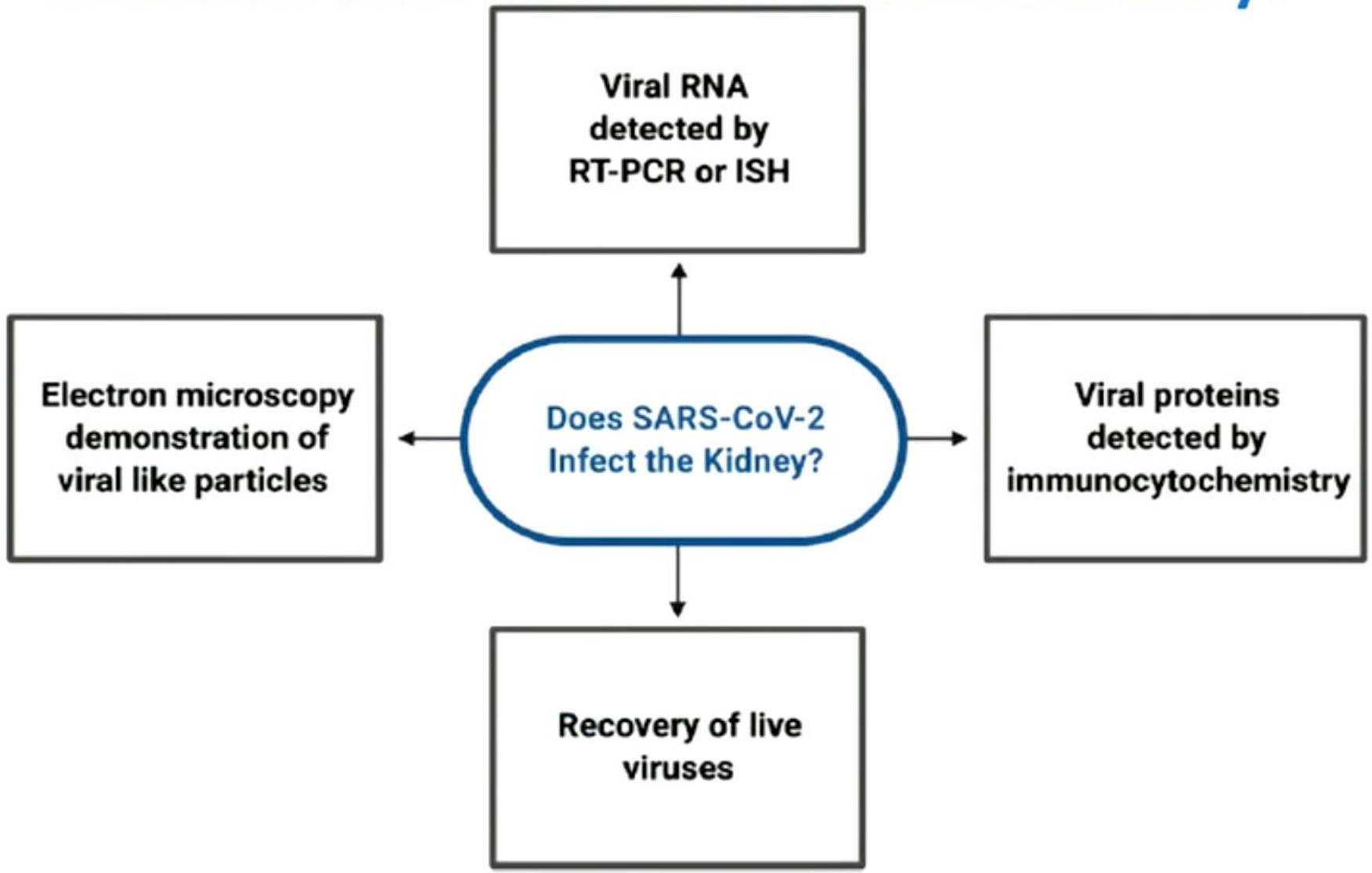

Clinical Kidney Journal, 2021, vol. 14, Suppl 1, i30–i39

doi: 10.1093/ckj/sfab003
Advance Access Publication Date: 24 January 2021
CKJ Review

CKJ REVIEW

Pathology of COVID-19-associated acute kidney injury

Purva Sharma[1,2], Jia H. Ng [1], Vanesa Bijol[2,3], Kenar D. Jhaveri[1,2] and Rimda Wanchoo[1,2]

[1]Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, NY, USA, [2]Glomerular Center at Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, NY, USA and [3]Department of Pathology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, NY, USA

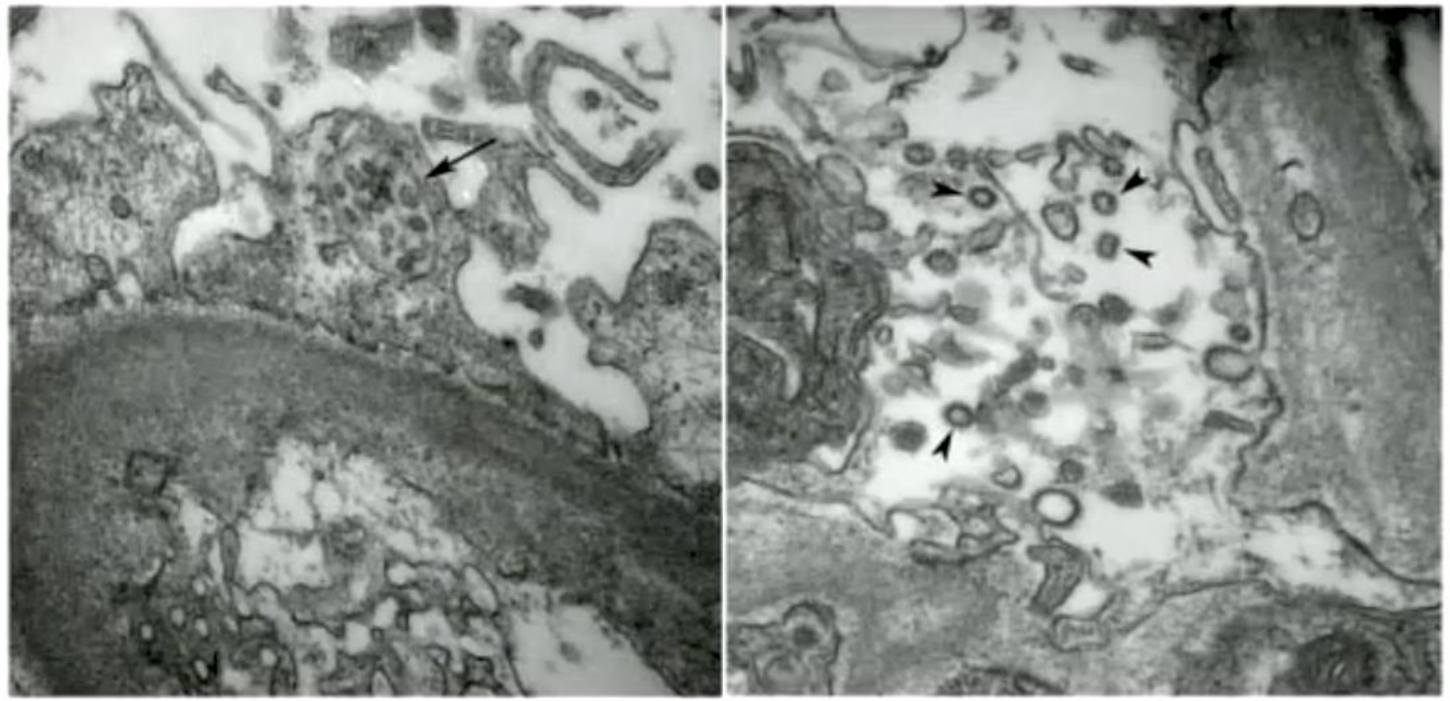

FIGURE 1: Electron micrograph to the left shows a microvesicular body within the podocyte cytoplasm (black arrow; original magnification ×40 000) and the electron micrograph to the right shows multiple clathrin-coated vesicles in the endothelial cell cytoplasm (black arrowheads; original magnification ×50 000). Both structures have been often confused with viral particles.

What is the Site of Viral Entry?
Is it ACE-2?

Evidence That C-19 Can Infect the Kidney?

> medRxiv. 2020 Sep 18;2020.09.16.20190694. doi: 10.1101/2020.09.16.20190694. Preprint

KIM-1/TIM-1 is a Receptor for SARS-CoV-2 in Lung and Kidney

Takaharu Ichimura, Yutaro Mori, Philipp Aschauer, Krishna M Padmanabha Das, Robert F Padera, Astrid Weins, Mahmoud L Nasr, Joseph V Bonventre

PMID: 32995803 PMCID: PMC7523142 DOI: 10.1101/2020.09.16.20190694

Evidence That C-19 Can Infect the Kidney?

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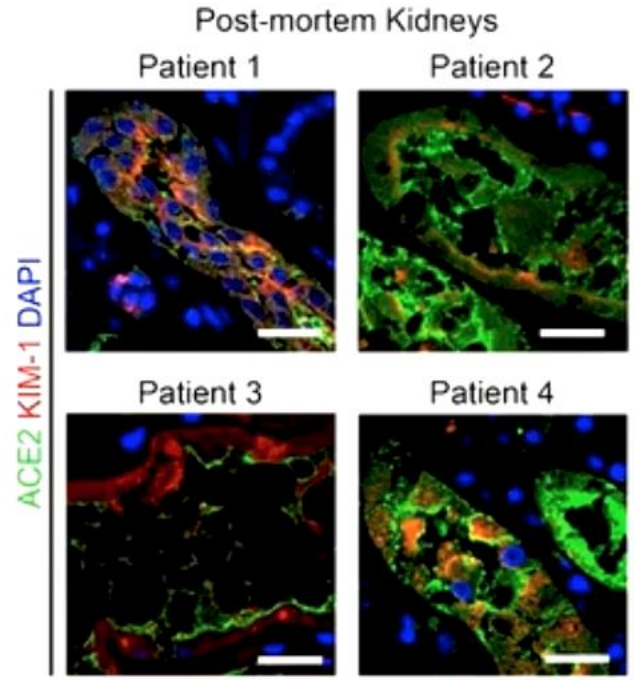
- KIM-1 is a receptor for SARS-CoV-2 with a high affinity interaction with the receptor binding domain of the virus S1 subunit of the spike protein
- KIM-1 dependent uptake by lung and kidney cells can be inhibited by anti-KIM-antibodies
- This may have important implications for viral entry, triggering of the cytokine storm, and/or inactivation of the virus



COVID-19 Associated Glomerular Disease

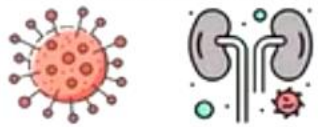
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

METHODS

6 hospitalized patients of recent African ancestry – 1/6 transplant recipient

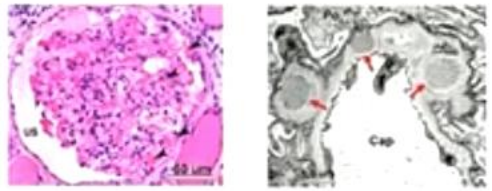
COVID-19 and proteinuric AKI



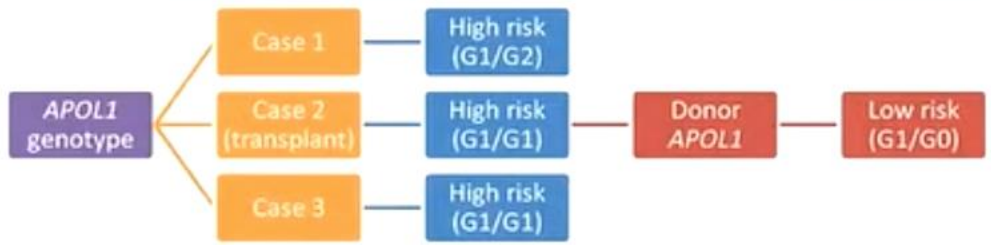
Underwent biopsy and *APOL1* genotyping

OUTCOME

Mild respiratory symptoms, 1/6 had ICU stay, 2/6 had hemodialysis



Collapsing Glomerulopathy and Podocytopathy with Tubulo-reticular inclusions



3/3 patients tested had high risk *APOL1* genotype.
The transplant recipient had high risk and donor had low risk *APOL1* genotype

Conclusion: COVID-19 associated proteinuric kidney injury with collapsing FSGS and/or podocytopathy may be linked to high risk *APOL1* genotype.

doi: 10.1681/ASN.2020060804

AJKD

Original Investigation

Multicenter Clinicopathologic Correlation of Kidney Biopsies Performed in COVID-19 Patients Presenting With Acute Kidney Injury or Proteinuria

Shreeram Akilesh, Cynthia C. Nast, Michifumi Yamashita, Kammi Henriksen, Vivek Charu, Megan L. Troxell, Neeraja Kambham, Erika Bracamonte, Donald Houghton, Naila I. Ahmed, Chyi Chyi Chong, Bijin Thajudeen, Shehzad Rehman, Firas Khoury, Jonathan E. Zuckerman, Jeremy Gitomer, Parthassarathy C. Raguram, Shanza Mujeeb, Ulrike Schwarze, M. Brendan Shannon, Iris De Castro, Charles E. Alpers, Behzad Najafian, Roberto F. Nicosia, Nicole K. Andeen, and Kelly D. Smith

Setting & Participants: We identified 14 native and 3 transplant kidney biopsies performed for cause in patients with documented recent or concurrent SARS-CoV-2 infection treated at 7 large hospital systems in the United States.

Conclusions: Cases of even symptomatically mild COVID-19 were accompanied by acute kidney injury and/or heavy proteinuria that prompted a diagnostic kidney biopsy. Although acute tubular injury was seen among most of them, uncommon pathology such as collapsing glomerulopathy and acute endothelial injury were detected, and most of these patients progressed to irreversible kidney injury and dialysis.

Multicenter Clinicopathologic Correlation of Kidney Biopsies Performed in COVID-19 Patients Presenting With AKI or Proteinuria

Setting

7 large referral centers in US

N = 17

9 female, 8 male
8 Black, 5 Hispanic

14 native kidney
3 allograft kidney

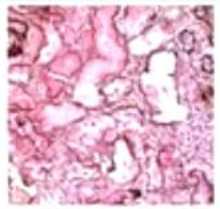
Clinical Presentation

N = 14 (82%) with MILD COVID-19 symptoms (eg cough, fatigue)

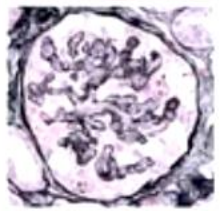
Kidney disease manifested within 1 week of COVID-19

Indication for biopsy:
N = 15 (88%) AKI
N = 11 (65%) Proteinuria

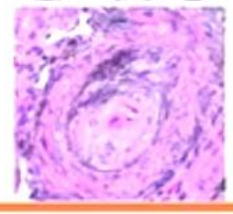
Pathologic Findings



Acute tubular injury
N = 15 (88%)



Collapsing glomerulopathy
N = 7 (41%)

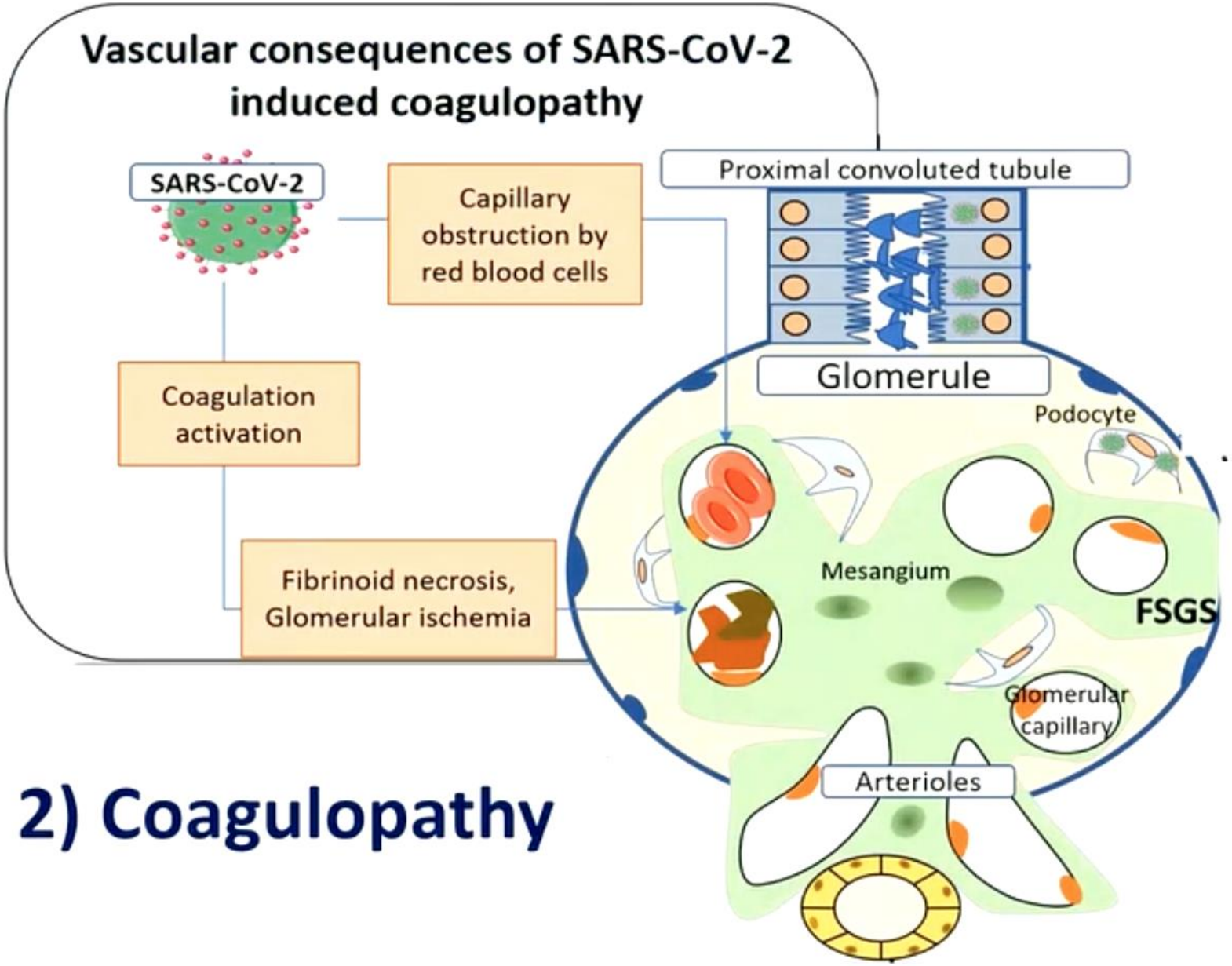


Thrombotic microangiopathy
N = 6 (35%)

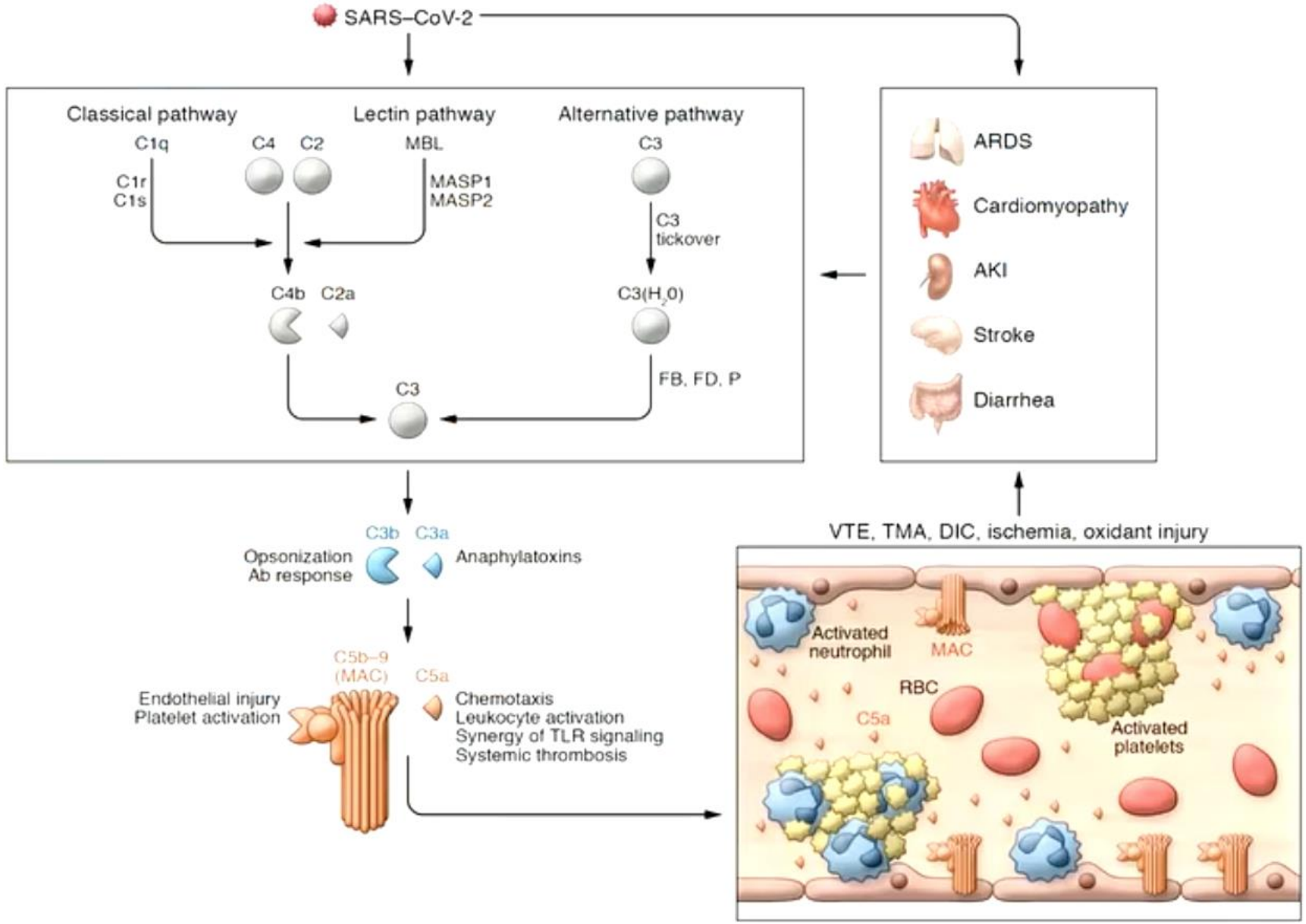
CONCLUSION: Even with mild COVID-19 disease, patients can present with AKI and/or proteinuria. Collapsing glomerulopathy and thrombotic microangiopathy are frequently seen and can lead to irreversible injury requiring dialysis.

Shreeram Akilesh, Cynthia C. Nast, Michifumi Yamashita, et al (2020)
@AJKDonline | DOI: 10.1053/j.ajkd.2020.10.001

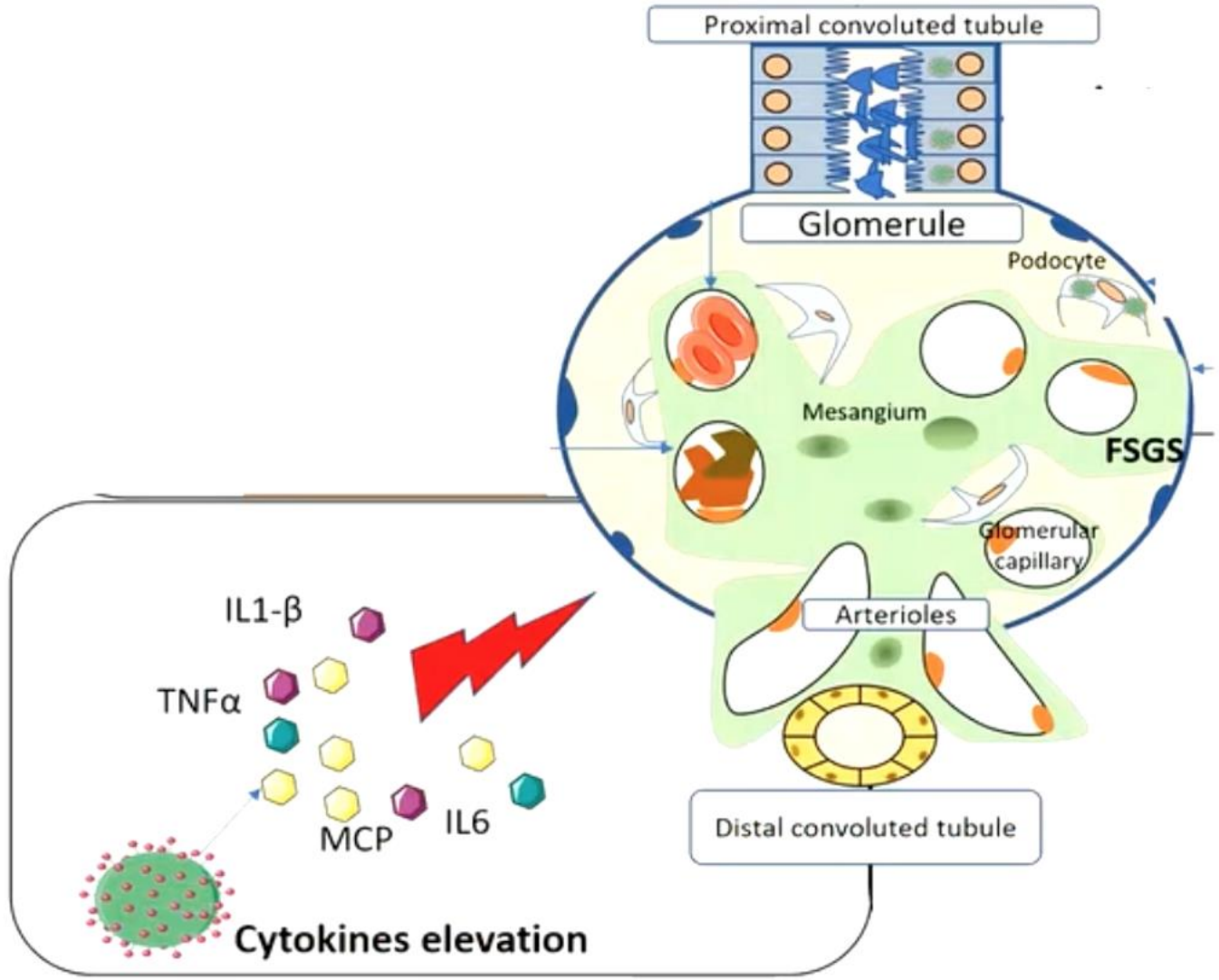
AJKD



2) Coagulopathy


SARS–CoV-2
Classical pathway
C1q
C1r
C1s
C4
C2
C4b
C2a
Lectin pathway
MBL
MASP1
MASP2
Alternative pathway
C3
C3 tickover
C3(H2O)
FB, FD, P
C3
C3b
C3a
Opsonization
Ab response
Anaphylatoxins
C5b–9 (MAC)
C5a
Endothelial injury
Platelet activation
Chemotaxis
Leukocyte activation
Synergy of TLR signaling
Systemic thrombosis
ARDS
Cardiomyopathy
AKI
Stroke
Diarrhea
VTE, TMA, DIC, ischemia, oxidant injury
Activated neutrophil
MAC
RBC
C5a
Activated platelets

The Storm.....

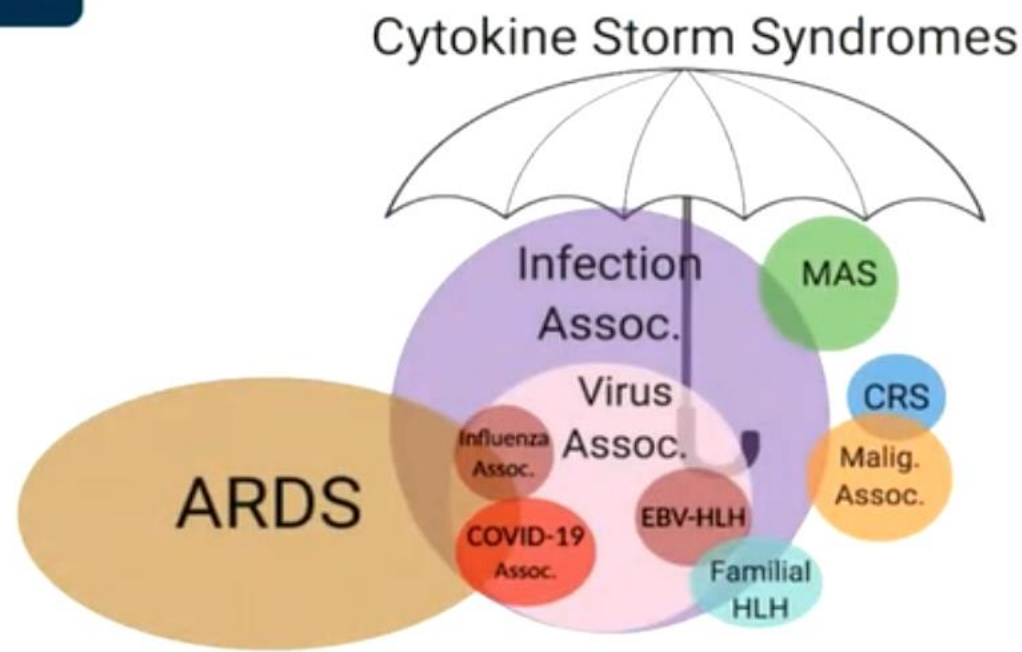

Proximal convoluted tubule
Glomerule
Podocyte
Mesangium
FSGS
Glomerular capillary
Arterioles
Distal convoluted tubule
IL1-β
TNFα
MCP
IL6
Cytokines elevation

Cytokine Storm Syndromes

An Umbrella Term

Types of cytokine storm syndromes

- In hematology, these are known as MAS
- In oncology, leukemias and lymphomas may cause cytokine storms
  - CAR T-cell therapy: CRS
- Familial/inherited HLH: affects ~1 in 50,000 live-births
- Infection-induced HLH: caused by viral infections



Clinical and Laboratory Features of CSS
Reported Events in Patients With COVID-19

HLH-04 Criteria	H-Score	Ferritin:ESR ratio	COVID-19 Features
Fever	Fever		Yes
Splenomegaly	Splenomegaly		Unknown
	Hepatomegaly		Unknown
Anemia	Anemia		Yes
Thrombocytopenia	Thrombocytopenia		Yes
Neutropenia	Neutropenia		Yes
Hypertriglyceridemia	Hypertriglyceridemia		Unknown
Hypofibrinogenemia	Hypofibrinogenemia		Yes
Hemophagocytosis	Hemophagocytosis		Unknown
Low NK cell activity			Unknown
Hyperferritinemia	Hyperferritinemia	Hyperferritinemia	Yes
Elevated soluble CD25	Elevated soluble CD25		Yes
	Elevated serum GGT		Unknown, but AST and ALT ↑
	Underlying immunosuppression		Some with HIV infection
		Falling ESR	Unknown

Cron RQ, et al. *J Rheumatol.* 2020;47:639-642.

The Cytokine Storm -- What Exactly Does It Mean?

The use of this term can vary, but it is generally used by some medical professionals to help

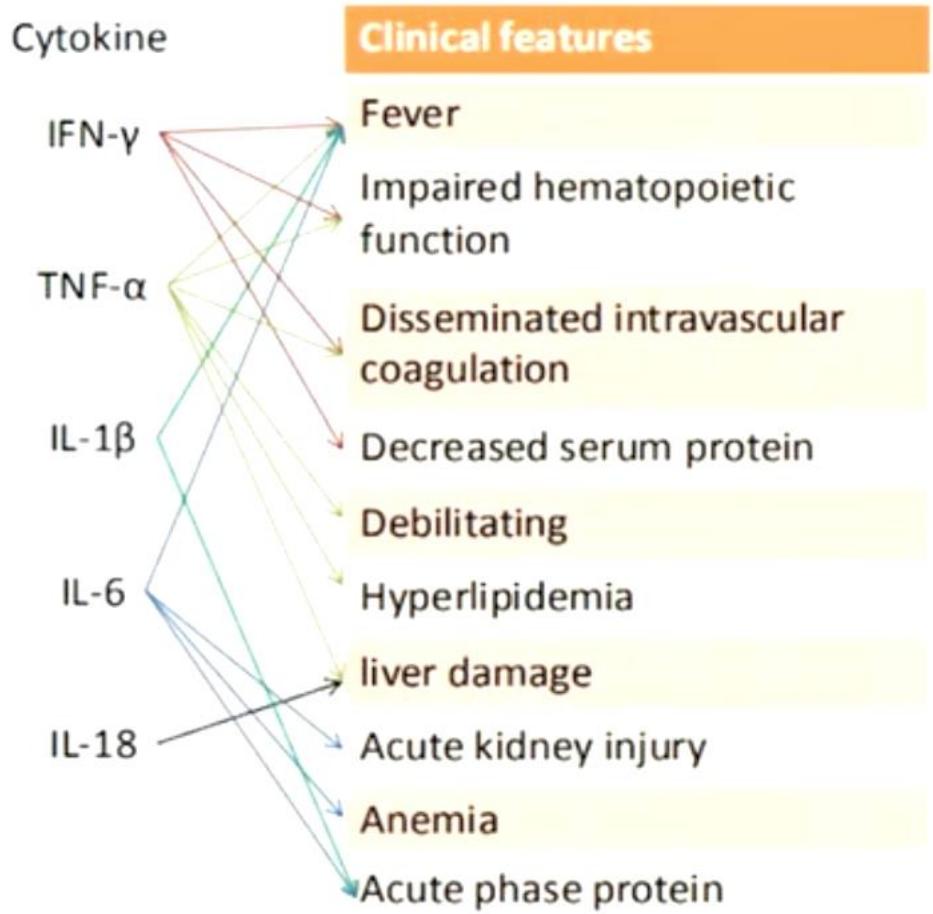
- Categorize patients and therapeutic strategies
- Classify academic findings and research

Others argue that this terminology may be inaccurate, specifically with respect to COVID-19

- IL-6 levels may not be elevated in patients
- May be best described as a hyperinflammatory state

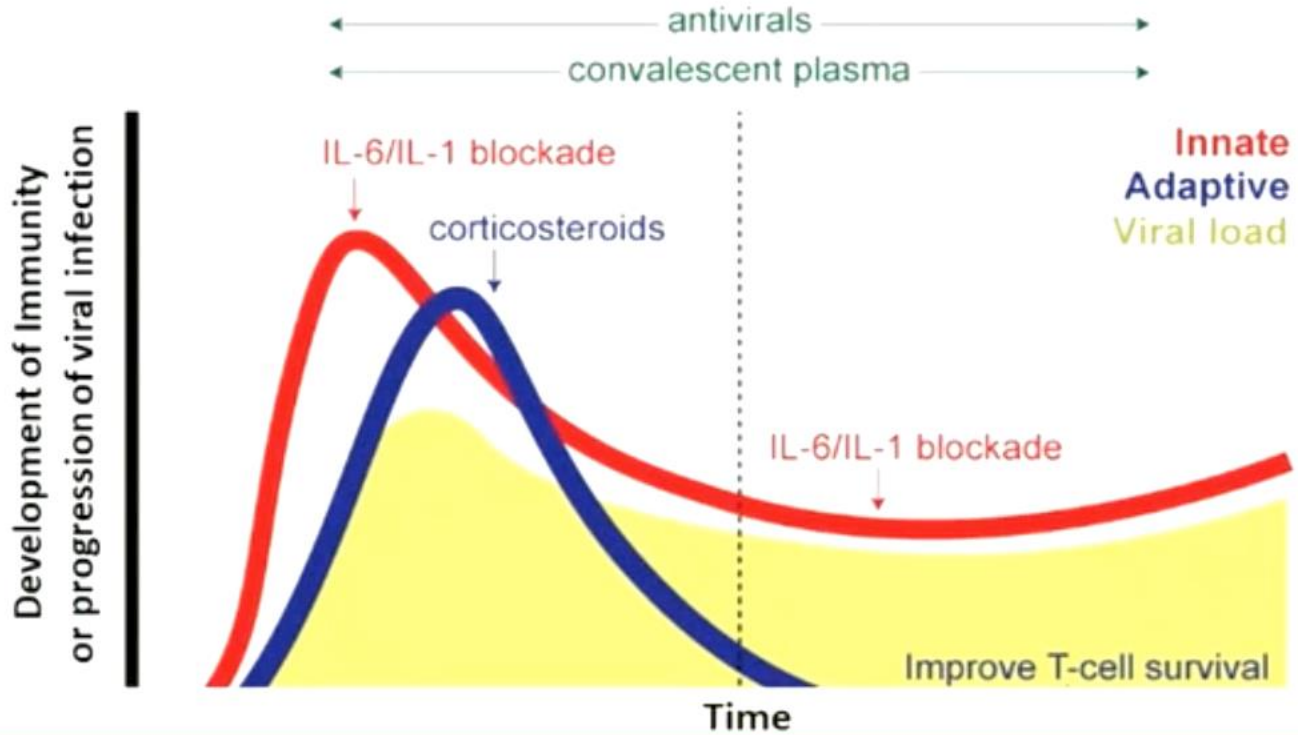
The COVID-19 Cytokine Signature

- **May help identify developing signs that could be used to monitor/treat patients**
- **Cytokine storm → produces immunopathogenic damage to tissues and organs**
  - **This phenomenon occurs even if the immune response seeks to eradicate the virus**
- **Complex network of interactions that make it difficult to target a single cytokine**



Sun X, et al. *Cytokine Growth Factor Rev.* 2020;53:38-42.

Clinical Phases of Disease in Relation to CSS



The measurement or detection of elevated levels of a given cytokine does not make it a good therapeutic target alone; more research is needed to begin developing targeted approaches based on clinical findings

Vardhana SA, et al. *J Exp Med*. 2020;217:1-10.

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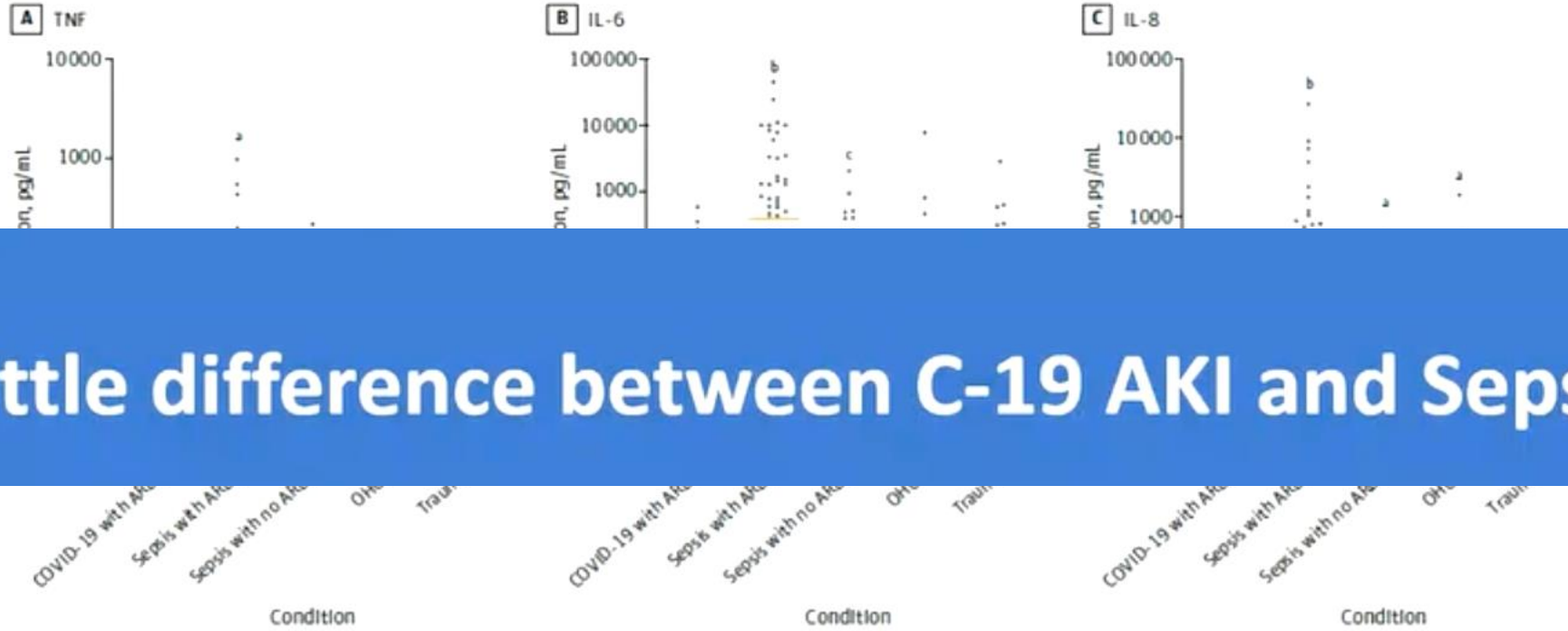
Research Letter

September 3, 2020

Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions

Matthijs Kox, PhD[1]; Nicole J. B. Waalders, BSc[1]; Emma J. Kooistra, BSc[1]; et al

Figure. Cytokine Levels in Critically Ill Patients With Coronavirus Disease 2019 (COVID-19) and Other Conditions



Little difference between C-19 AKI and Sepsis

Plasma concentrations of tumor necrosis factor (TNF) (A), IL-6 (B), and IL-8 (C) in patients with COVID-19 and acute respiratory distress syndrome (ARDS) (n = 46), septic shock with ARDS (n = 51), septic shock without ARDS (n = 15), out-of-hospital cardiac arrest (OHCA; n = 30), and multiple traumas (n = 62).

Data are presented as scatter plots with red horizontal bars indicating the geometric mean levels.

[a] $P < .01$ vs COVID-19 with ARDS.

[b] $P < .001$ vs COVID-19 with ARDS.

[c] $P < .05$ vs COVID-19 with ARDS.

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Blood Purification

Review

Blood Purif 2021;50:17–27
DOI: 10.1159/000508125

Received: April 17, 2020
Accepted: April 23, 2020
Published online: May 26, 2020

Extracorporeal Blood Purification and Organ Support in the Critically Ill Patient during COVID-19 Pandemic: Expert Review and Recommendation

Claudio Ronco[a, b] Sean M. Bagshaw[c] Rinaldo Bellomo[d, e] William R. Clark[f]
Faeq Husain-Syed[g] John A. Kellum[h, i] Zaccaria Ricci[j] Thomas Rimmelé[k, l]
Thiago Reis[m, n] Marlies Ostermann[n]

Be Careful What You Wish For…?

Articles

Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial

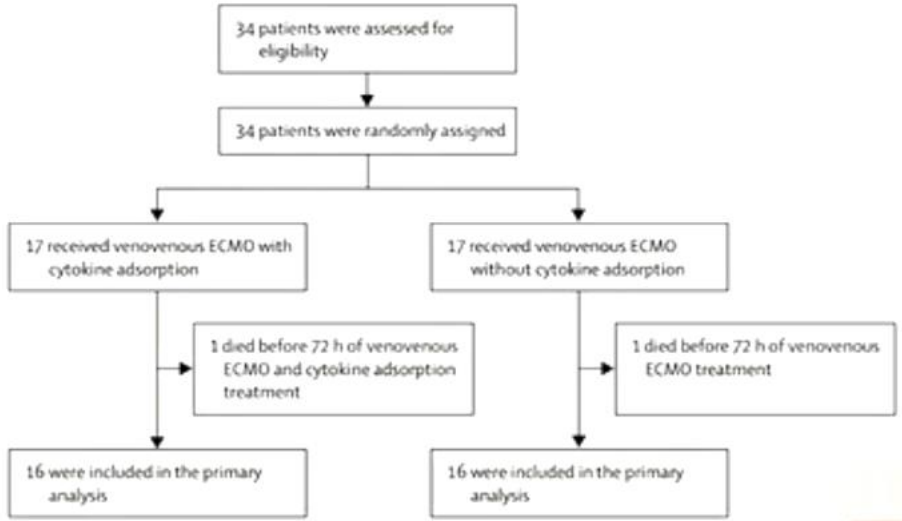
Alexander Supady, Enya Weber, Marina Rieder, Achim Lother, Tim Niklaus, Timm Zahn, Franziska Frech, Sissi Müller, Moritz Kuhl, Christoph Benk, Sven Maier, Georg Trummer, Annabelle Flügler, Kirsten Krüger, Asieb Sekandarzad, Peter Stachon, Viviane Zotzmann, Christoph Bode, Paul M Biever, Dawid Staudacher, Tobias Wengenmayer, Erika Graf, Daniel Duerschmied

Summary

Background We sought to clarify the benefit of cytokine adsorption in patients with COVID-19 supported with venovenous extracorporeal membrane oxygenation (ECMO).

Lancet Respir Med 2021

Published Online
May 14, 2021



	Cytokine adsorption group (n=17)	Control group (n=17)
Age, years	62·0 (54·0–71·5)	59·0 (43·5–66·5)
Sex		
Female	5 (29%)	4 (24%)
Male	12 (71%)	13 (76%)
Body-mass index, kg/m²	29·41 (24·69–33·20)	29·68 (26·41–36·48)
Laboratory values		
Interleukin-6, pg/mL	357·0 (177·4–1186·0)	289·0 (84·7–787·0)
C-reactive protein, mg/L	254·9 (148·0–374·4)	169·3 (128·6–342·2)
Procalcitonin, ng/mL	0·73 (0·50–1·84)	1·34 (0·37–5·98)
Ferritin, ng/mL	2172·0 (883·5–3706·0)*	1489·0 (938·5–2543·0)
Leukocytes, ×10³/µL	10·03 (8·22–19·92)	14·43 (8·40–16·48)
Neutrophils, ×10³/µL	9·12 (6·59–14·84)*	11·86 (7·18–13·92)
Lymphocytes, ×10³/µL	0·67 (0·44–1·15)*	0·59 (0·39–0·88)
Monocytes, ×10³/µL	0·51 (0·20–0·98)*	0·46 (0·22–0·90)
Willebrand factor antigen, %	603·5 (458·5–642·5)†	399·0 (362·0–542·5)*
D-dimers, mg/L FEU	9·1 (4·5–21·0)*	4·7 (3·4–13·5)
Scores		
SOFA	9·0 (8·0–10·0)	9·0 (7·0–10·5)
RESP	1·0 (0·5–2·0)	1·0 (0–3·5)
PRESERVE	4·0 (3·0–5·0)	4·0 (2·0–6·0)

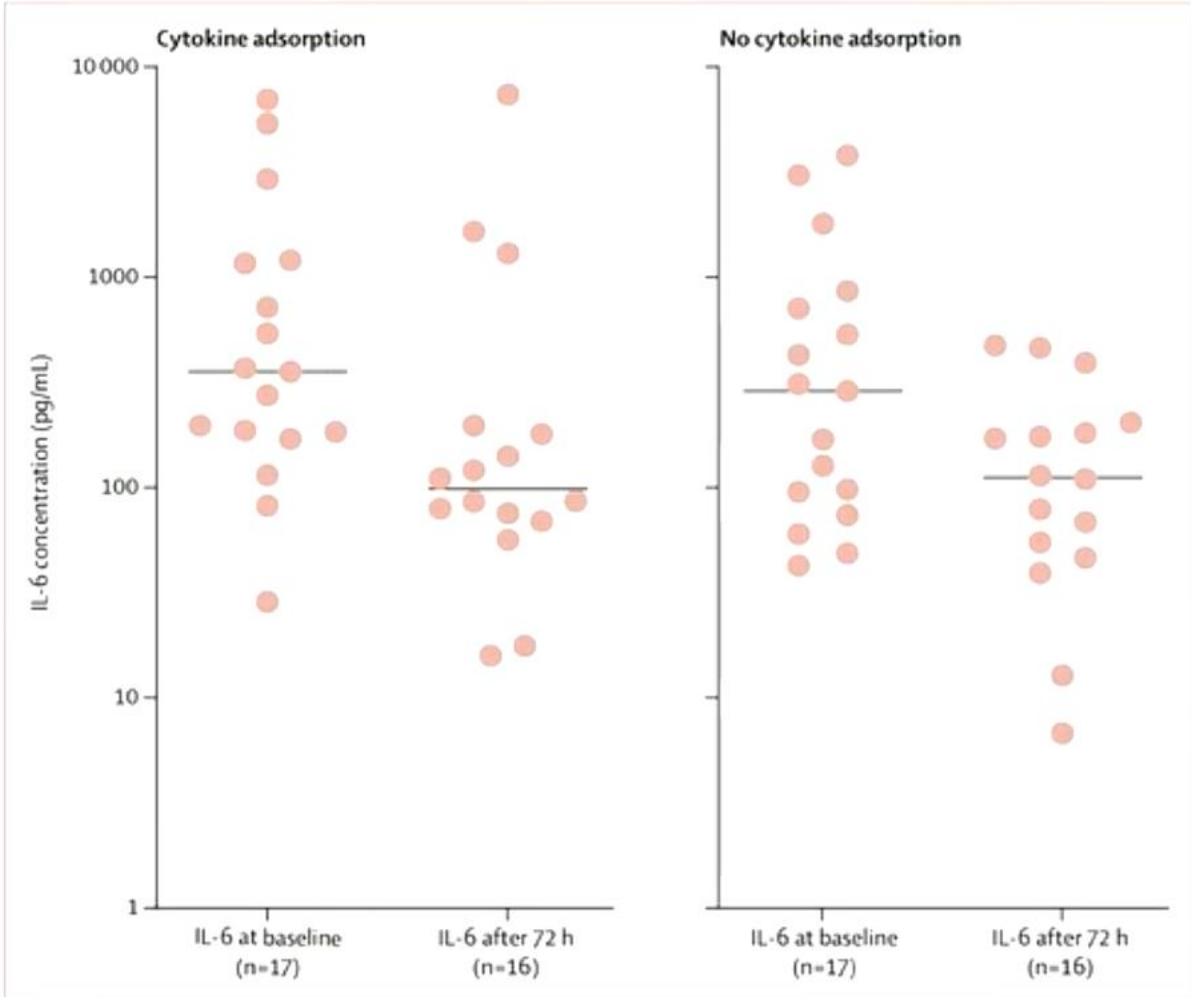


Figure 2: **IL-6 concentrations at baseline and after 72 h of venovenous ECMO with or without cytokine adsorption**

IL-6 values in the cytokine adsorption group and control group before and 72 h after initiation of venovenous ECMO are displayed on the logarithmic scale. Medians are shown as horizontal lines. No significant differences were detected between the two groups after 72 h of ECMO (p=0·54). IL-6=interleukin-6.

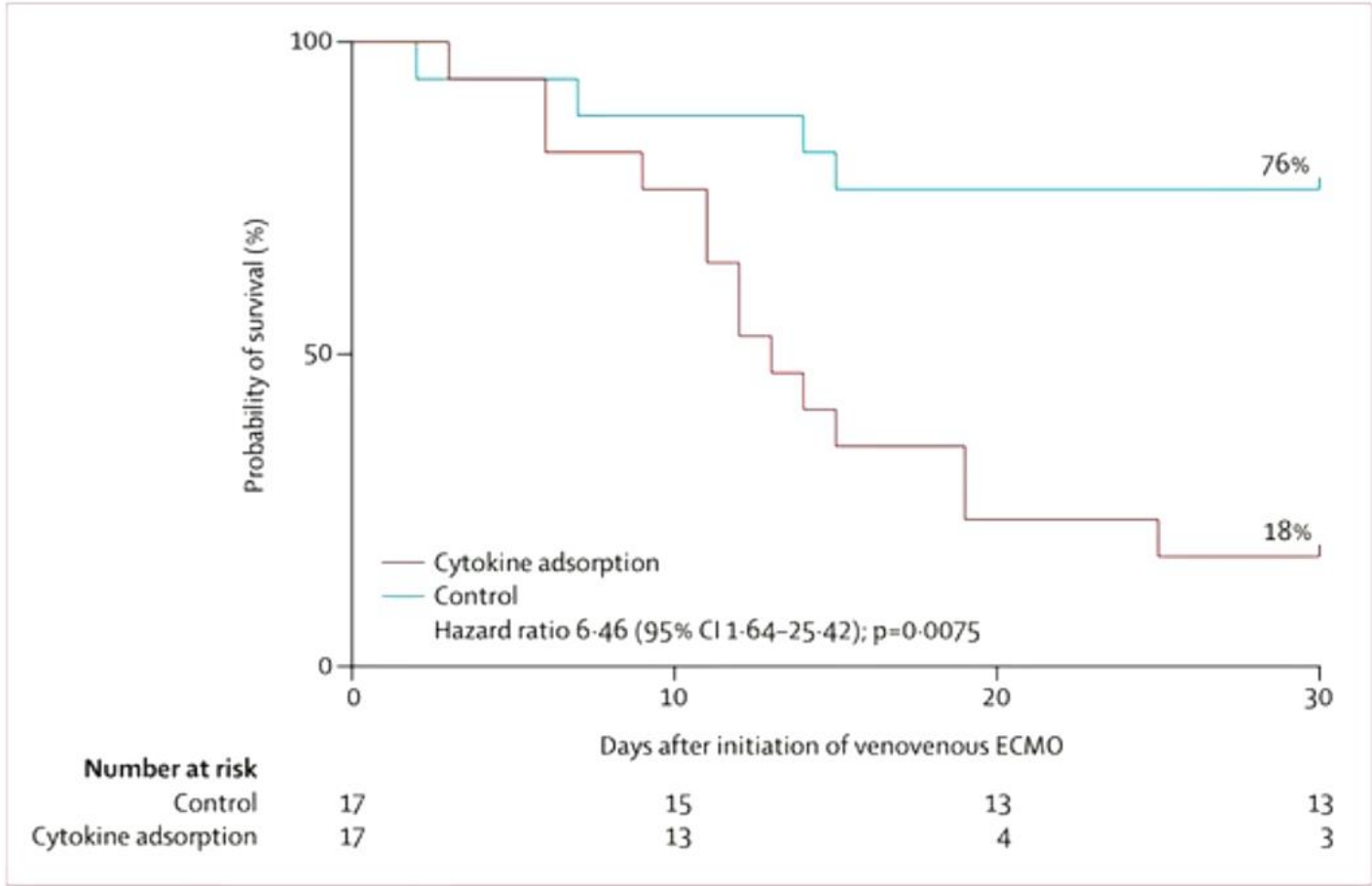
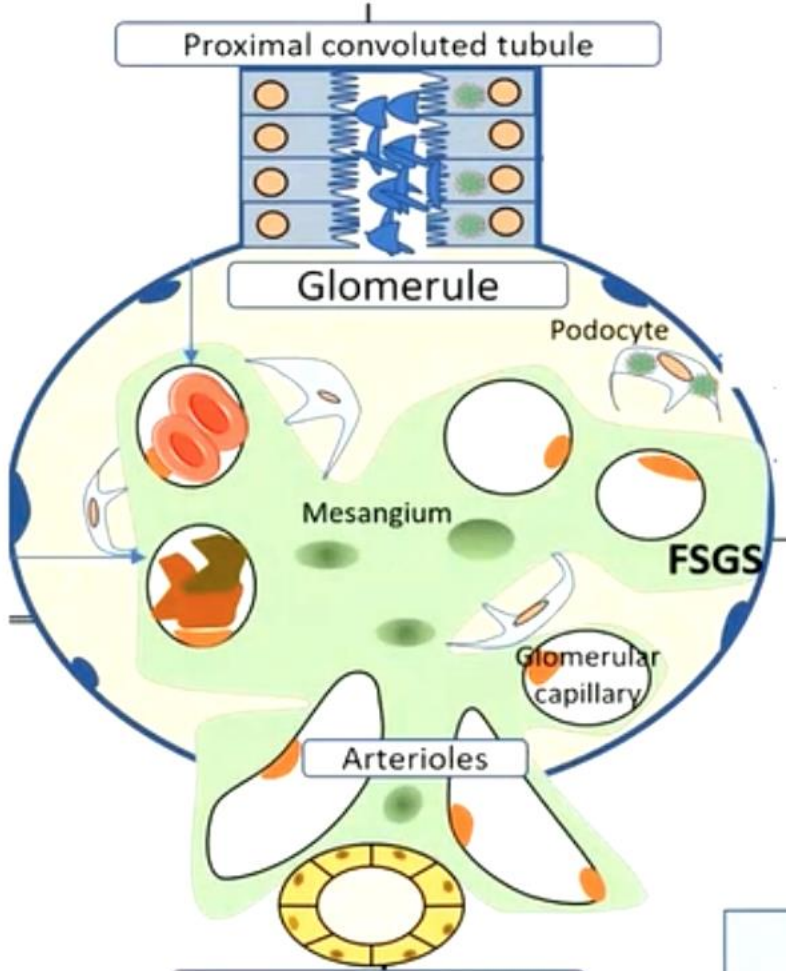


Figure 3: **Kaplan–Meier curves for survival in the cytokine adsorption group and control group**
Survival in the group receiving cytokine adsorption during the first 72 h of venovenous ECMO support was lower.
ECMO=extracorporeal membrane oxygenation.

How Do We Explain This?

- ? IL-6 relatively low levels
- Very variable IL-6 levels (heterogeneity)
- Removal of other Cytokines?
- Systemic levels ? less relevant than lung?
- ? Antibiotic/Drug Clearance
- ? Timing : Too late?
- ? Unknown interactions on immune system

4) Everything Else….



Lung/heart dysfunction

High level of PEEP

Nephrotoxic drugs

Fluid restriction

Haemodynamic instability

ICU

Unspecific kidney injury factors

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

kidney INTERNATIONAL

ISN 60 years

EDITORIAL | ARTICLES IN PRESS

Sepsis-Associated Acute Kidney Injury: Is COVID-19 different?

John A. Kellum • Mitra K. Nadim • Lui G. Forni

Published: September 09, 2020 • DOI: https://doi.org/10.1016/j.kint.2020.08.009

Etiology/Mechanism	Bacterial sepsis	COVID-19 sepsis	Comments
Systemic inflammation affecting multiple organs	+++	++	Corticosteroids have been shown to improve survival in COVID-19 while the effect in bacterial sepsis is only on reversal of shock
DAMPs released from injured tissue	+++	+++	Injured lung and also remote organs (e.g. muscle) may contribute DAMPs
PAMPs released from microorganisms	+++	?	Extensive involvement of the GI tract in some patients raises concern for translocation of bacteria/bacterial products
Thrombotic microangiopathy (TMA)	+	++	The TMA in COVID-19 appears to be unique from DIC, TTP, and HUS.
Nephrotoxic drugs	+++	+++	Different agents are used in the two syndromes
Direct viral infection of tubular epithelial cells	N/A	+	The full extent of this pathobiological mechanism is still unknown
Cardiac dysfunction and/or reduced pre-load	+	++	COVID-19 may directly affect the heart and high PEEP +/- volume depletion may impair venous return

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Acute Kidney Injury in Hospitalized Patients with and without COVID-19: A Comparison Study

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

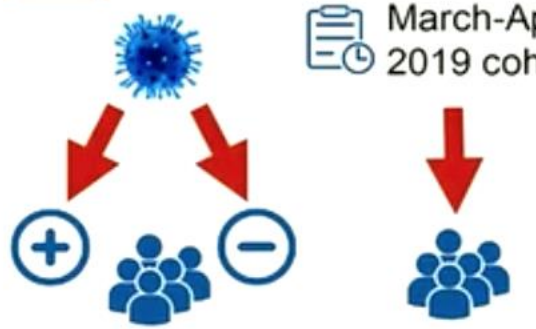
METHODS

Retrospective study

3 Bronx New York Hospitals

March 11 - April 26, 2020

March-April 2019 cohort



n=3345 n=1265 n=9859

RESULTS

Incidence	(+)	(−)	
AKI	56.9%	37.2%	25.1%
RRT	4.9%	1.6%	0.9%
Severe AKI			
Renal recovery	42.3%	68.0%	63.9%
RRT dependence	5.6%	12.0%	16.4%
Death	52.1%	19.6%	19.6%

Admission Predictors of Stage 2 or 3 AKI

Age
Black race
Male sex
Diabetes mellitus
Nursing home resident
Respiratory rate
White blood cell count
Neutrophil/lymphocyte ratio
Lactate dehydrogenase

CONCLUSION COVID-19 was associated with a high incidence of AKI and RRT. COVID-19 positive patients with severe AKI had >2.6 fold higher mortality compared to those without COVID-19 and severe AKI.

doi: 10.1681/ASN.2020040509

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GUIDANCE
shift

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

CONSENSUS STATEMENT

OPEN

Check for updates

COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup

Mitra K. Nadim[1], Lui G. Forni[2,3], Ravindra L. Mehta[4], Michael J. Connor Jr[5], Kathleen D. Liu[6], Marlies Ostermann[7], Thomas Rimmelé[8], Alexander Zarbock[9], Samira Bell[10], Azra Bihorac[11], Vincenzo Cantaluppi[12], Eric Hoste[13], Faeq Husain-Syed[14], Michael J. Germain[15], Stuart L. Goldstein[16], Shruti Gupta[17], Michael Joannidis[18], Kianoush Kashani[19], Jay L. Koyner[20], Matthieu Legrand[21], Nuttha Lumlertgul[7,22], Sumit Mohan[23,24], Neesh Pannu[25], Zhiyong Peng[26], Xose L. Perez-Fernandez[27], Peter Pickkers[28], John Prowle[29], Thiago Reis[30,31], Nattachai Srisawat[22,32], Ashita Tolwani[33], Anitha Vijayan[34], Gianluca Villa[35], Li Yang[36], Claudio Ronco[30,37] and John A. Kellum[38]✉

Box 1 | **Potential Risk Factors for COVID-19 AKI**

Demographic risk factors

- Older age
- Diabetes mellitus
- Hypertension
- Cardiovascular disease or congestive heart failure
- High body mass index
- Chronic kidney disease
- Genetic risk factors (e.g. *APOL1* genotype; *ACE2* polymorphisms)
- Immunosuppressed state
- Smoking history

Risk factors for AKI at admission

- Severity of COVID-19
- Degree of viraemia
- Respiratory status
- Non-respiratory organ involvement, e.g. diarrhoea
- Leukocytosis
- Lymphopaenia
- Elevated markers of inflammation, e.g. ferritin, C-reactive protein, D-dimers
- Hypovolaemia/Dehydration
- Rhabdomyolysis
- Medication exposure, e.g. angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs), statins, nonsteroidal anti-inflammatory drugs (NSAIDs)

Risk factors for AKI during hospitalization

- Nephrotoxins (medications, contrast exposure)
- Vasopressors
- Ventilation, high positive end-expiratory pressure
- Fluid dynamics (fluid overload or hypovolaemia)

Box 1 | **Potential Risk Factors for COVID-19 AKI**

- Genetic risk factors (e.g. *APOL1* genotype; *ACE2* polymorphisms)

- Severity of COVID-19
- Degree of viraemia

Recommendations : Management

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Therapy	Rationale	Recommendation
Standard measures		
Standard measures based on AKI risk and stage	Prevention and management depend on the risk and stage of AKI	Strategies based on KDIGO and other relevant guidelines are appropriate for risk- and stage-based prevention and management of COVID-19 AKI (ungraded)
Measurement of kidney function	The measurement of kidney function is necessary for precise clinical assessment of risk and stage of AKI. Serum creatinine and urine output are the current gold standards for the evaluation of kidney function, although neither is kidney specific or sensitive for detection of early kidney injury	We recommend monitoring kidney function using a minimum serum creatinine and urine output with careful consideration of the limitations of both (evidence level: 1B)
Haemodynamic optimization	Hypovolaemia, hypotension, and vasoplegia may occur in patients with COVID-19. Fluid and vasopressor resuscitation using dynamic assessment of cardiovascular status may reduce the risk of renal injury and respiratory failure	We recommend individualized fluid and haemodynamic management based on dynamic assessment of cardiovascular status (evidence level: 1B)
Fluid management	The composition of crystalloids for volume expansion is important. Individual trials in non-COVID patients have shown reduced risk of AKI with use of balanced fluids for initial volume expansion, especially in sepsis	We recommend using balanced crystalloids as initial management for expansion of intravascular volume in patients at risk of or with COVID-19 AKI unless an indication for other fluids exists (evidence level: 1A)

Recommendations : Management

58 ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

Therapy	Rationale	Recommendation
Standard measures		
Glucose management	Insulin resistance and a hypercatabolic state are common in COVID-19 and contribute to hyperglycaemia	We suggest monitoring for hyperglycaemia and use of intensive glucose-lowering strategies in high-risk patients (evidence level: 2C)
Nephrotoxin management	Nephrotoxins are frequently prescribed in patients with COVID-19. The risks and benefits of these medications and their alternatives need to be closely and frequently assessed. This includes assessment of NSAID use	We recommend limiting nephrotoxic drug exposure where possible and with careful monitoring when nephrotoxins are required (evidence level: 1B)
Use of contrast media	Some studies have challenged the relevance of contrast media toxicity in critically ill patients; furthermore, sodium bicarbonate and N-acetylcysteine have not been shown to prevent contrast-media-associated AKI	We recommend optimization of intravascular volume status as the only specific intervention to prevent contrast-media-associated AKI (evidence level: 1A)

Conclusions:

BMJ 2020;369:m1963 doi: 10.1136/bmj.m1963 (Published 26 May 2020)

PRACTICE

GUIDELINES

Covid-19 and acute kidney injury in hospital: summary of NICE guidelines

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NICE National Institute for Health and Care Excellence

COVID-19 rapid guideline: acute kidney injury (AKI)

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Admission or transfer

In all patients with suspected or confirmed COVID-19, assess for AKI and record:

- Medical history and comorbidities, including any factors that further increase the risk of AKI
- Fluid status by clinical examination
- Fluid status by fluid balance
- Full blood count
- Serum urea, creatinine and electrolytes

Stop medicines that can cause or worsen AKI, unless essential

Managing fluid status

Aim for optimal fluid status (euvolaemia) in all patients

- If there is hypovolaemia, and fluid needs cannot be met orally or enterally, give IV fluids as part of a protocol to restore and maintain optimal fluid status
- Review the patient's IV fluid management plan daily: base choice of fluids on biochemistry results and fluid status
- Do not routinely offer loop diuretics, but consider them for treating fluid overload
- Manage hyperkalaemia according to local protocols

Ongoing monitoring

Record and monitor:

- Fluid status by clinical examination daily
- Fluid status by fluid balance daily
- Serum urea, creatinine and electrolytes at least every 48 hours, or more often if clinically indicated

Indicators of AKI

Detect AKI using the NHS England AKI algorithm, or any of:

- An increase in serum creatinine of 26 micromol/litre or more in 48 hours
- An increase of 50% or more in serum creatinine known or presumed to have occurred in the past 7 days
- A fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours

AKI detected

- Do urinalysis for blood, protein and glucose
- Do imaging if urinary tract obstruction is suspected

Referral

Refer patients for further specialist advice if:

- Further tests or imaging are needed because of diagnostic uncertainty
- Urinalysis results show possible COVID-19-induced kidney damage or other intrinsic renal disease
- Fluid management needs are complex
- AKI is worsening despite initial management or has not resolved in 48 hours
- There are usual indications for renal replacement therapy, particularly if there is no urine output

Factors that further increase the risk of AKI:

- Chronic kidney disease
- Heart failure
- Liver disease
- Diabetes
- History of AKI
- Age 65 years or over

Assessments:

Fluid status by clinical examination:
For example, peripheral perfusion, capillary refill, pulse rate, blood pressure, postural hypotension, jugular venous pressure, pulmonary or peripheral oedema

Fluid status by fluid balance:
Fluid intake, urine output and weight

Electrolytes:
Sodium, potassium and bicarbonate

Useful links:

NICE has produced a guideline on acute kidney injury: prevention, detection and management

For help with fluid management, see the algorithms and composition of commonly used crystalloids in the NICE guideline on intravenous fluid therapy in adults in hospital

See Think Kidneys guidelines for medicines optimisation in patients with acute kidney injury

Thanks for Your Attention