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COVID-19 in Heart Transplant recipients

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CHU de Liège

No disclosure

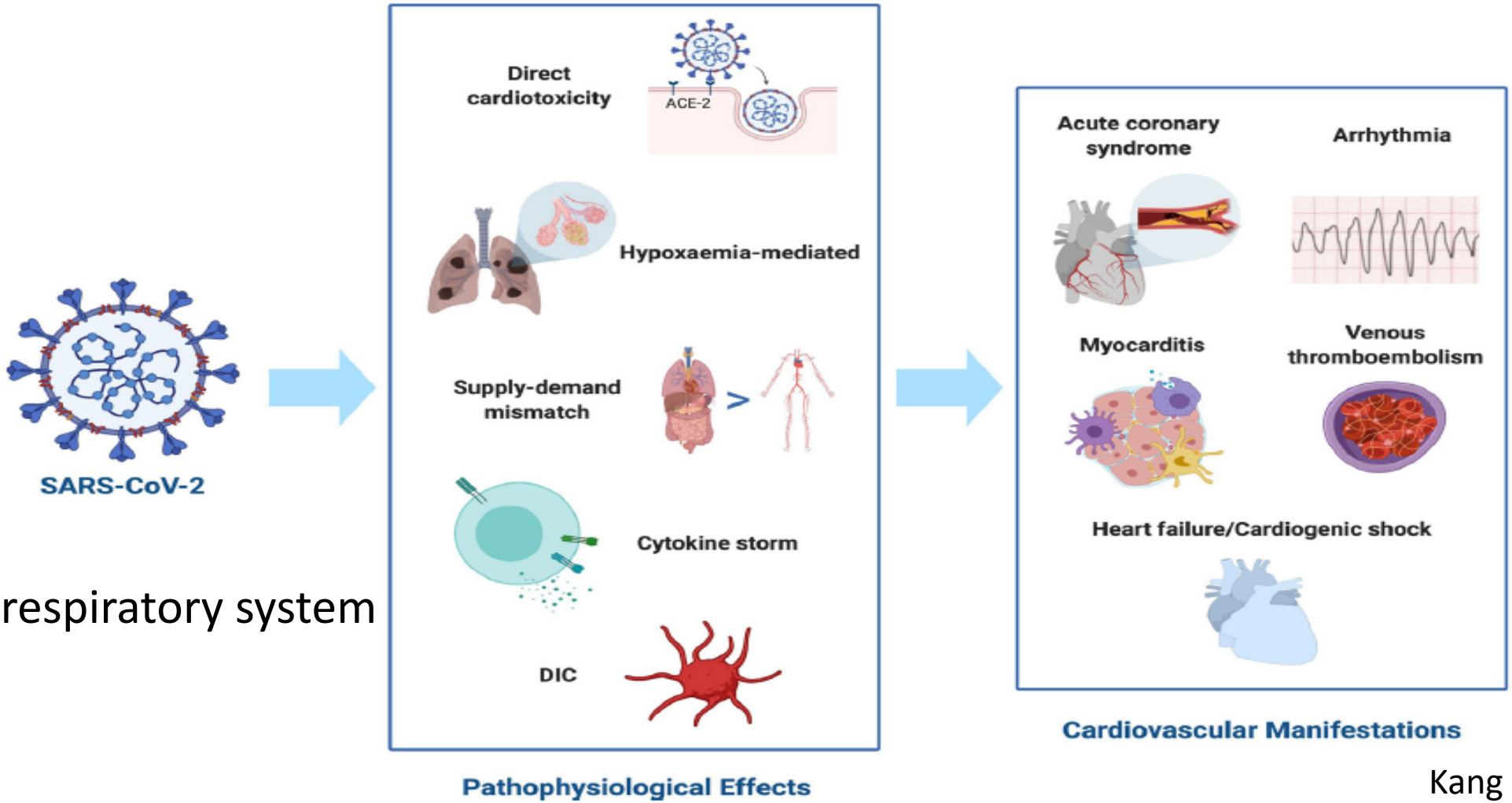
Introduction

- Solid organ transplant recipients (SOTR) and particularly heart transplant recipients (HTR) are at high risk of severe COVID-19 infection due to their comorbidities and immunosuppressed state

- Early in the pandemic, impact of COVID-19 on SOTR was not well established (limited data)

- There were early reports suggesting similar clinical presentation of the disease in SOTR and the general population

Possible Mechanisms of Cardiovascular Injury Due to Covid-19



Beyond the respiratory system

Kang Y, Heart 2020

Reference number and publication year	Country	Type of study	Patient profile (age in years, sex)	Diagnosis
Ahluwalia et al. [11]	USA	Retrospective study, single center	26 M, 49 M, 50 M, 58 M, 61 F	Heart transplant
Ammirati et al. [12]	Italy	Case report	61 M	Heart kidney transplant
Berg et al. [28]	USA	Case report	66 M	Heart transplant
Ballout et al. [29]	USA	Retrospective study, single center	21 M, 23 M, 32 M	Heart kidney transplant, Heart transplant
Bosch et al. [13]	Germany	Case report	48 M	Heart transplant
Carraffa et al. [14]	Italy	Retrospective study, single center	50 F, 62 M, 65 M, 69 M, 71 M, 82 M	Heart transplant
Decker et al. [15]	Germany	Case report	62 M	Heart transplant
Felldin et al. [30]	Sweden	Retrospective study, multiple centers	22 M, 50 M, 62 F, 64 M, 65 M, 67 M	Heart kidney transplant, Heart transplant
Fernandez-Ruiz et al. [31]	Spain	Retrospective study, single center	38 M, 63 M, 64 M, 67 M	Heart transplant
Fried et al. [25]	USA	Case report	51 M	Heart kidney transplant
Fung et al. [16]	USA	Case report	42 M	Heart transplant
Gozzi-Silva et al. [32]	Brazil	Retrospective study, single center	55 F, 62 M	Heart transplant
Guerreiro et al. [33]	Brazil	Retrospective study, single center	22 F, 31 M, 55 M	Heart transplant
Holzhauser et al. [7]	USA	Retrospective study, single center	59 F, 75 M	Heart transplant
Hsu et al. [27]	USA	Case report	39 M	Heart kidney transplant
Isik et al. [34]	Turkey	Case report	55 M	Heart transplant
Jang et al. [17]	USA	Case report	67 M	Heart transplant
Kadosh et al. [18]	USA	Case report	56 M	Heart transplant
Kates et al. [10]	USA	Case report	73 M	Heart transplant
Li et al. [26]	China	Retrospective study, single center	43 M, 51 M	Heart transplant
Lima et al. [19]	USA	Retrospective study, single center	45 M, 62 M, 67 M, 68 M, 68 F,	Heart transplant
Mangiameli et al. [35]	France	Case report	55 M	Heart transplant
Martens et al. [36]	Belgium	Case report	60 M	Heart transplant
Mathies et al. [9]	Germany	Case report	77 M	Heart transplant
Mattioli et al. [8]	Italy	Case report	62 M	Heart transplant
Schreiber et al. [37]	USA	Case report	67 F	Heart transplant
Schtruk et al. [20]	Brazil	Retrospective study, single center	47 M, 54 M	Heart transplant
Soriano et al. [38]	Brazil	Retrospective study, single center	35 F, 37 M, 44 M, 50 M, 51 M, 52 F, 67 M, 69 M, 73 M, 74 M, 79, M	Heart transplant
Soquet et al. [21]	France	Case report	23 F	Heart transplant
Sperry et al. [22]	USA	Case report	37 M	Heart transplant
Tchana-Sato et al. [39]	Belgium	Retrospective study, single center	56 F, 59 M	Heart transplant
Vaidya et al. [23]	USA	Case report	61 M	Heart transplant
Vilaro et al. [24]	USA	Case report	50 M	Heart kidney transplant

Case reports and limited case series at the beginning of the pandemic

Clinical course and challenging management of early COVID-19 infection after heart transplantation: case report of two patients

Vincent Tchana-Sato[1*†], Arnaud Ancion[2†], Julien Tridetti[2], Natzi Sakalihasan[1], Marie Pierre Hayette[3], Olivier Detry[4], Philippe Delvenne[5], Philippe Amabili[6], Marc Senard[6], Olivier Hougrand[5], Delphine Szecel[1], Jean-Paul Lavigne[1], Elie Minga Lowampa[1], Charlotte Ponte[1], Isabelle Maquoi[6], Philippe Morimont[7], Melissa Van Den Bulck[7], Marie Helene Delbouille[4], Jean Olivier Defraigne[1†] and Patrizio Lancellotti[2†]

Abstract

Background: There are limited data on Coronavirus disease 2019 (COVID-19) in solid organ transplant patients, especially in heart transplant recipients, with only a few case reports and case series described so far. Heart transplant recipients may be at particular high risk due to their comorbidities and immunosuppressed state.

Case presentation: This report describes the clinical course and the challenging management of early COVID-19 infection in two heart transplant recipients who tested positive for the SARS-CoV-2 virus in the perioperative period of the transplant procedure. The two patients developed a severe form of the disease and ultimately died despite the initiation of an antiviral monotherapy with hydroxychloroquine coupled with the interruption of mycophenolate mofetil.

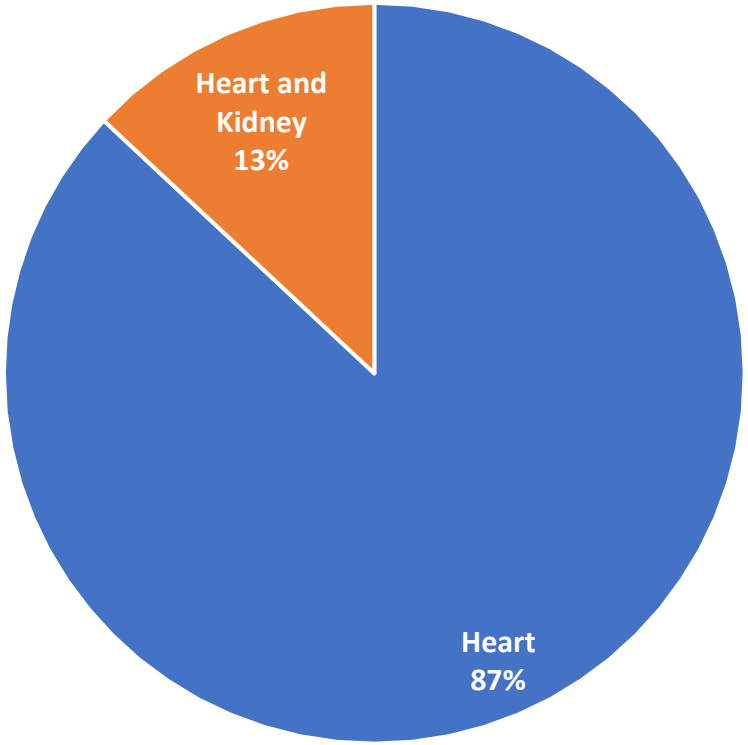
Conclusions: These two cases illustrate the severity and poor prognosis of COVID-19 in the perioperative period of a heart transplant. Thorough screening of donors and recipients is mandatory, and the issue of asymptomatic carriers needs to be addressed.

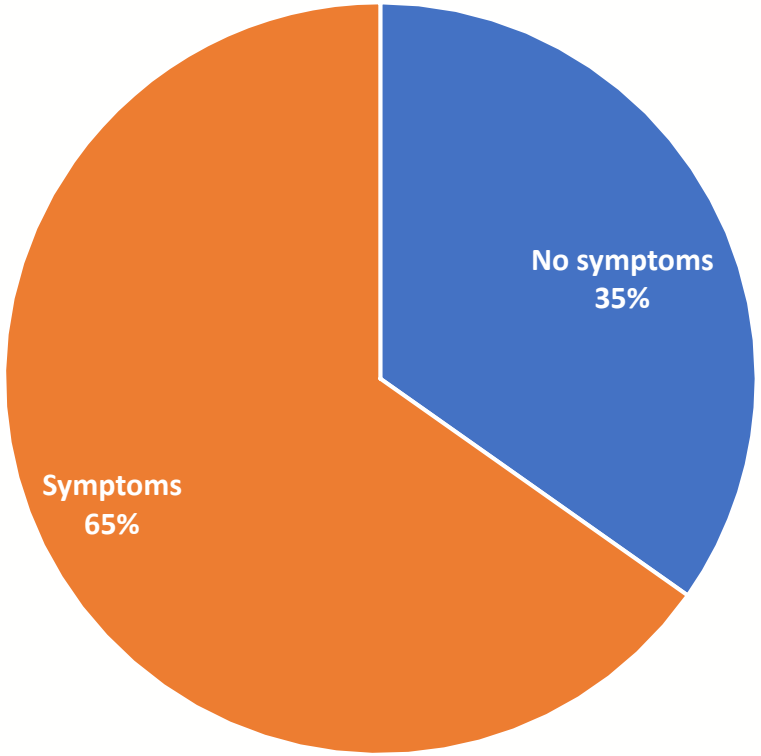
Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), Coronavirus disease 2019 (COVID-19), Heart transplantation, Asymptomatic carrier, Case report

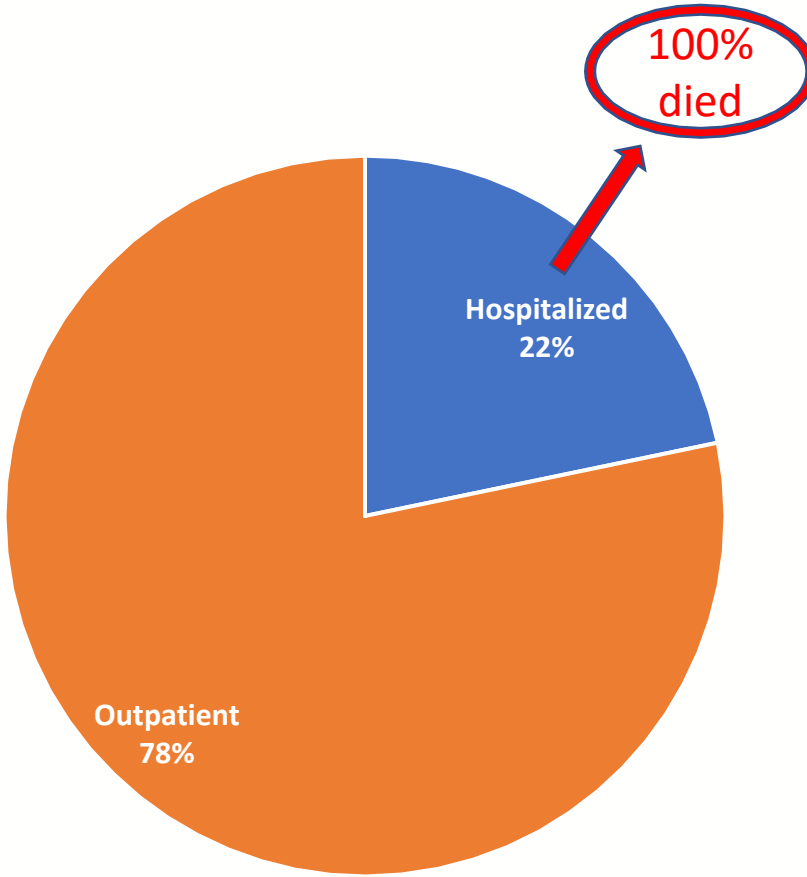
Tchana-sato et al.; BMC infectious disease 2O21

COVID-19 in HTR: CHU Liege

- From March 2020 to December 2021: 23 patients
- 4 women/ 19 men







Study	Year	Country	Date of inclusion	Sample size	Mortality
Cohorts					
Ahluwalia et al.	2020	USA	March 10–May 15	5	20%
Al-Darzi et al.	2020	USA	March 13–May 1	6	0%
Bottio 1 et al.	2020	Italy	February 21–June 30	47	30%
Bottio 2 et al.	2020	Italy	July 1–August 30	6	0%
Caraffa et al.	2020	Italy	Not reported	6	33%
Cavagna et al.	2020	Italy	February	5	40%
Coll et al.	2020	Spain	February 20–July 13	69	22%
Felldin et al.	2020	Sweden	February 21–June 22	6	33%
Garcia-Cosio et al.	2020	Spain	February 28–April 28	13	23%
Hoek et al.	2020	The Netherlands	Not reported	4	25%
Iacovoni et al.	2020	Italy	February–March	26	27%
Kates et al.	2020	USA	March 7–May 14	57	14%
Ketcham et al.	2020	USA	March 21–April 22	13	15%
Latif et al.	2020	USA	March 1–April 24	28	25%
Lima et al.	2020	USA	March 14–April 19	5	0%
Rivinius et al.	2020	Germany	March–June	21	33%
Singhvi et al.	2020	USA	March 1–May 15	22	23%
Trapani et al.	2020	Italy	February 21–June 22	53	36%
Case reports	2020	Several countries[a]	January–June	23	4%

Barcelona, Spain

KEYWORDS
COVID-19, heart transplantation, systematic review

Coronavirus disease 2019 in heart transplant recipients: Risk factors, immunosuppression, and outcomes

BACKGROUND: COVID-19 continues to inflict significant morbidity and mortality, particularly on patients with preexisting health conditions. The clini
suppression regimen in heart transplant recipient
METHODS: We included the first 99 heart transp
and followed patients until resolution. We coll
ies, vital signs, and outcomes for included patie
baseline with severe disease were compared us
transplant.
RESULTS: The median age was 60 years, 25% w
transplant to infection was 5.6 years. Overall,
remained asymptomatic. During the course of il
tinal symptoms were common. Tachypnea, oxy
markers were predictive of severe course. Age
use of the combination of calcineurin inhibito
more severe disease compared to the combina
(adjusted OR = 7.3, 95% CI 1.8-36.2). Among
infection, acute kidney injury was common and
CONCLUSIONS: We present the largest study to da
ing common atypical presentations and a high case fatality rate of 24% among hospitalized patients and 16% among symptomatic patients.

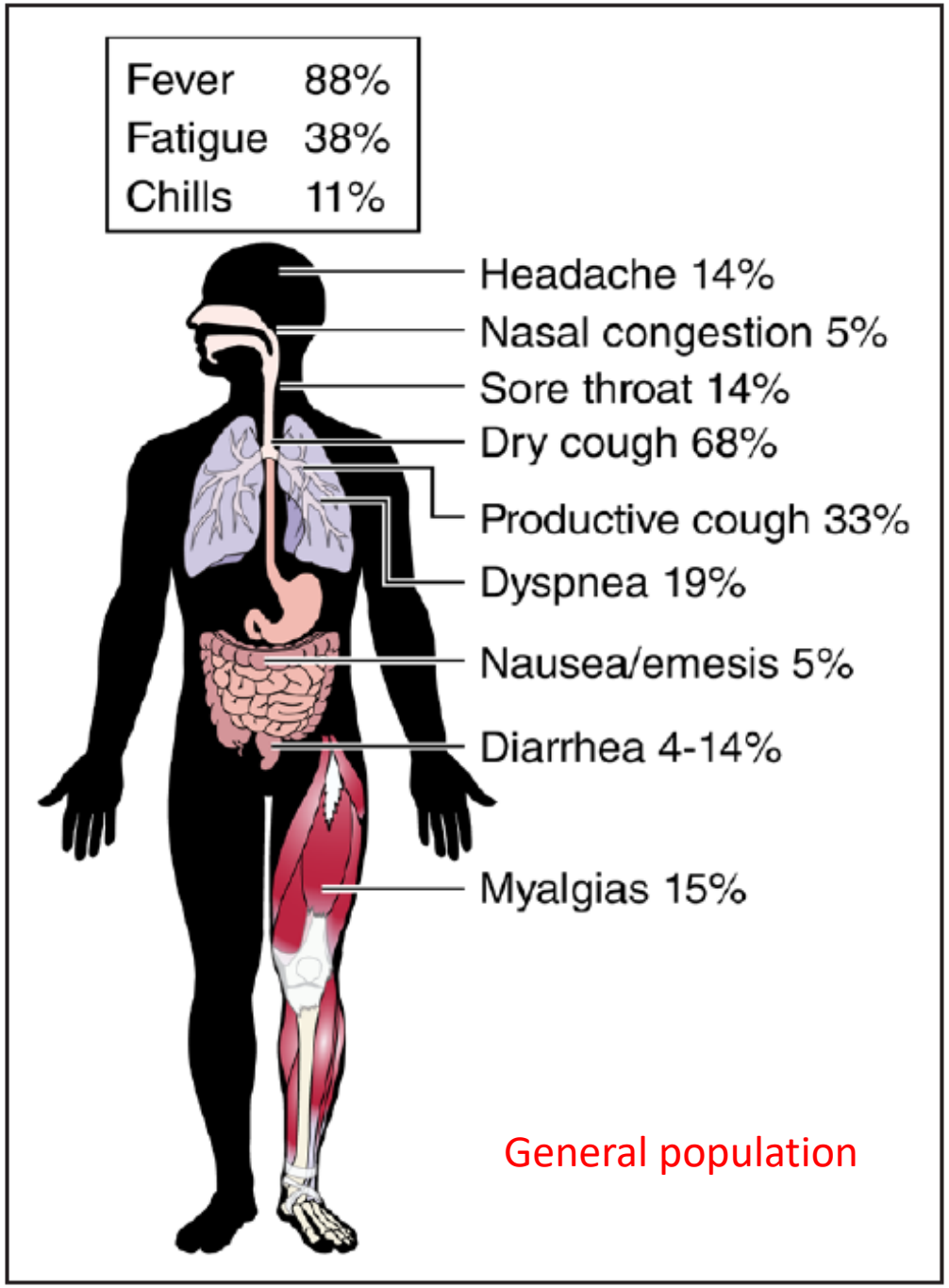
>42% of black transplant recipients

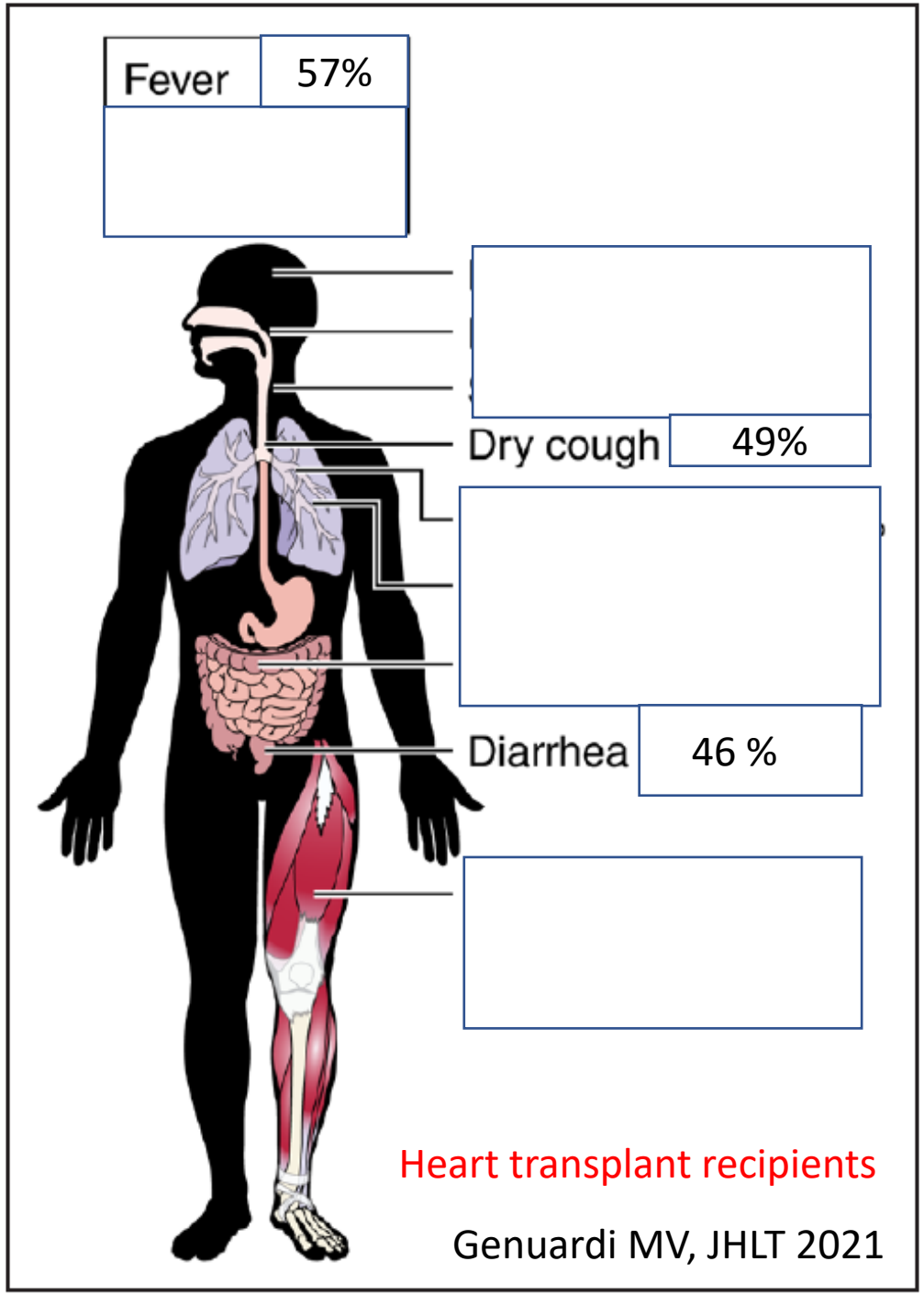
>Atypical symptoms are common

>Overall fatality rate of 15%

>Use of PSI and Prednisone associated with increased risk of severe disease

Genuardi MV, JHLT 2021


Fever 88%
Fatigue 38%
Chills 11%
Headache 14%
Nasal congestion 5%
Sore throat 14%
Dry cough 68%
Productive cough 33%
Dyspnea 19%
Nausea/emesis 5%
Diarrhea 4-14%
Myalgias 15%
General population


Fever 57%
Dry cough 49%
Diarrhea 46 %
Heart transplant recipients
Genuardi MV, JHLT 2021

IMMUNOSUPPRESSION MANAGEMENT

Society/Reference	Origin	Date	Guideline	Recommendation
British Transplantation Society [188]	UK	January 2021	Guidance on the management of transplant recipients diagnosed as having or suspected of having COVID-19	Outpatients: - Stop antiproliferative agents (MMF/azathioprine) - Review total burden of immunosuppression and consider reduction of CNIs - High or increased dose steroid is NOT recommended at this stage Hospitalized patients: - Stop antiproliferative agents (MMF/azathioprine) Consider reducing or stopping CNIs - Dexamethasone 6 mg daily for 10 d Patients requiring ventilatory support: - Stop antiproliferative agents (MMF/azathioprine) - Dramatically reduce or stop CNIs - Consider dexamethasone, as above
International Society of Heart and Lung Transplantation [189]	International	February 2021	Guidance from the International Society of Heart and Lung Transplantation regarding the SARS-CoV-2 pandemic	- For transplant recipients, consider holding MMF, mTOR inhibitors, or azathioprine while admitted with moderate/severe illness.
Transplantation Society [190]	International	March 2021	Guidance on Coronavirus	- Dexamethasone 6 mg daily for up to 10 d can be
American Association for the Study of Liver Diseases [191]	US	March 2021	Clinical Best Practice Advice for Hepatology and Liver transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement	- Consider lowering the overall level of immunosuppression, particularly antimetabolite dosages (eg, azathioprine or MMF) based on general principles for managing infections in transplant recipients and to decrease the risk of superinfection. - Monitor kidney function and CNI levels. - Adjust immunosuppressive medications based on severity of COVID-19 and risk of graft rejection and renal injury.
Canadian Society of Transplantation [192]	Canada	April 2021	Consensus guidance and recommendations for organ donation and transplantation services during COVID-19 pandemic	- Based on current evidence, we suggest a temporary adjustment of maintenance immune suppression for hospitalized patients with severe COVID-19. - Data on optimal immune-suppression adjustment in patients with COVID-19 are lacking, may vary, and may not be required depending on disease severity and physician judgment.
American Society of Transplantation [193]	US	June 2021	2019-nCoV (Coronavirus): FAQs for Organ Transplantation	- The impact of immunosuppression on COVID-19 is not currently known but decreasing immunosuppression may be considered for infected recipients who have not had recent rejection episodes. - Many providers have decreased or discontinued cell cycle inhibitors or reduced CNI levels, but comparative data regarding these interventions are not yet available. - Whether adjunctive corticosteroid therapy for patients with severe ARDS may be beneficial is also unknown.

Disparity in the recommendations >> Need for more studies to clarify the best approach

Quante M, Transplantation proceedings 2021

Efficacy of the COVID-19 vaccine in heart transplant recipients: what we know and what we ignore

Maria Generosa Crespo-Leiro[1]*, Eduardo Barge-Caballero[1], and Finn Gustafsson[2]

[1]Department of Cardiology, Complexo Hospitalario Universitario A Coruña (CHUAC), Instituto de Investigación Biomedica A Coruña (INIBIC), Centro de Investigacion Biomedica en Red Cardiovascular (CIBERCV), A Coruña, Spain; and [2]Department of Cardiology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

In summary, the immunological response to the vaccine is probably somewhat more complex than measuring antibody titre, as the T-cellular response and studies with long-term clinical follow-up are needed to assess efficacy in both preventing COVID-19 and severe disease, and safety. The issue of the third dose is a promising possibility and given the preliminary encouraging experience, deserves to be explored in future research. Also, the modification of immunosuppression, e.g. withdrawal of MMF in order to achieve a greater response, is a very controversial issue as the risk– benefit in relation to triggering rejection related to changes in immunosuppression is still unknown. Meanwhile, continued research, taking advantage of all available clinical data and evaluating immunogenicity, clinical efficacy and exploring strategies to improve vaccine response in vulnerable populations, such as HT patients, will help us to understand and control the COVID-19 pandemic.

European Journal of Heart Failure, 2021

Table 1 Summary of clinical studies assessing the immune response to mRNA vaccinations in the setting of solid organ transplantation.

Publication	Study population	Vaccine, dose	Outcome	Results, comments
Boyarsky et al[9]	658 SOT recipients	Pfizer-BioNTech and Moderna, one dose	*Antibody response	357/658 (54%) with detectable IgG at median 29 days after Dose 2. Older age, use of mycophenolate, use of Pfizer BioNTech vaccine and time since transplant was associated with negative serology.
Yi et al[10]	145 KT recipients	Pfizer-BioNTech and Moderna, one dose	Antibody response (unknown test)	8/145 (5.5%) with anti-spike IgG measured prior to Dose 2. No additional data re: timing from vaccine dose, risk factors.
Benotmane et al[11]	242 KT recipients	Moderna, one dose	*Antibody response	26/242 (10.7%) with detectable anti-spike IgG at 28 days from Dose 1. Shorter time from transplant and use of anti-thymocyte globulin, mycophenolate and steroids associated with negative serology by univariate analysis.
Grupper et al.[13]	136 KT recipients	Pfizer BioNTech, two doses	Antibody response	51/136 (37.5%) with detectable IgG at median 16 days after Dose 2. Negative serology associated with increasing age, pre-transplant dialysis duration, living donor, high dose steroids in previous 12 months, mycophenolate, triple immunosuppression, low lymphocyte count, higher serum creatinine and lower GFR by univariate analysis
Sattler et al[12]	39 KT recipients	Pfizer BioNTech, two doses	*Antibody and T-cell response	1/39 (2.6%) had IgG seroconversion at 8 days following Dose 2. Prevalence of spike specific CD4 cells was similar to controls 36/39 (92%), spike specific CD8 cell response only noted in 2/29 (5.13%) No alloreactivity noted.
Peled et al[14]	77 HT recipients	Pfizer BioNTech, two doses	*Antibody response	14/77 (18%) with detectable RBD IgG at mean 21 days following Dose 2. Mycophenolate use associated with lower odds of seroconversion in multivariate analysis. No serious adverse events noted by 41 days from Dose 2.
Havlin et al[15]	48 LT recipients	Pfizer BioNTech, two doses		

Aslam et al.; JHLT 2021

Immune paresis in SOT recipients

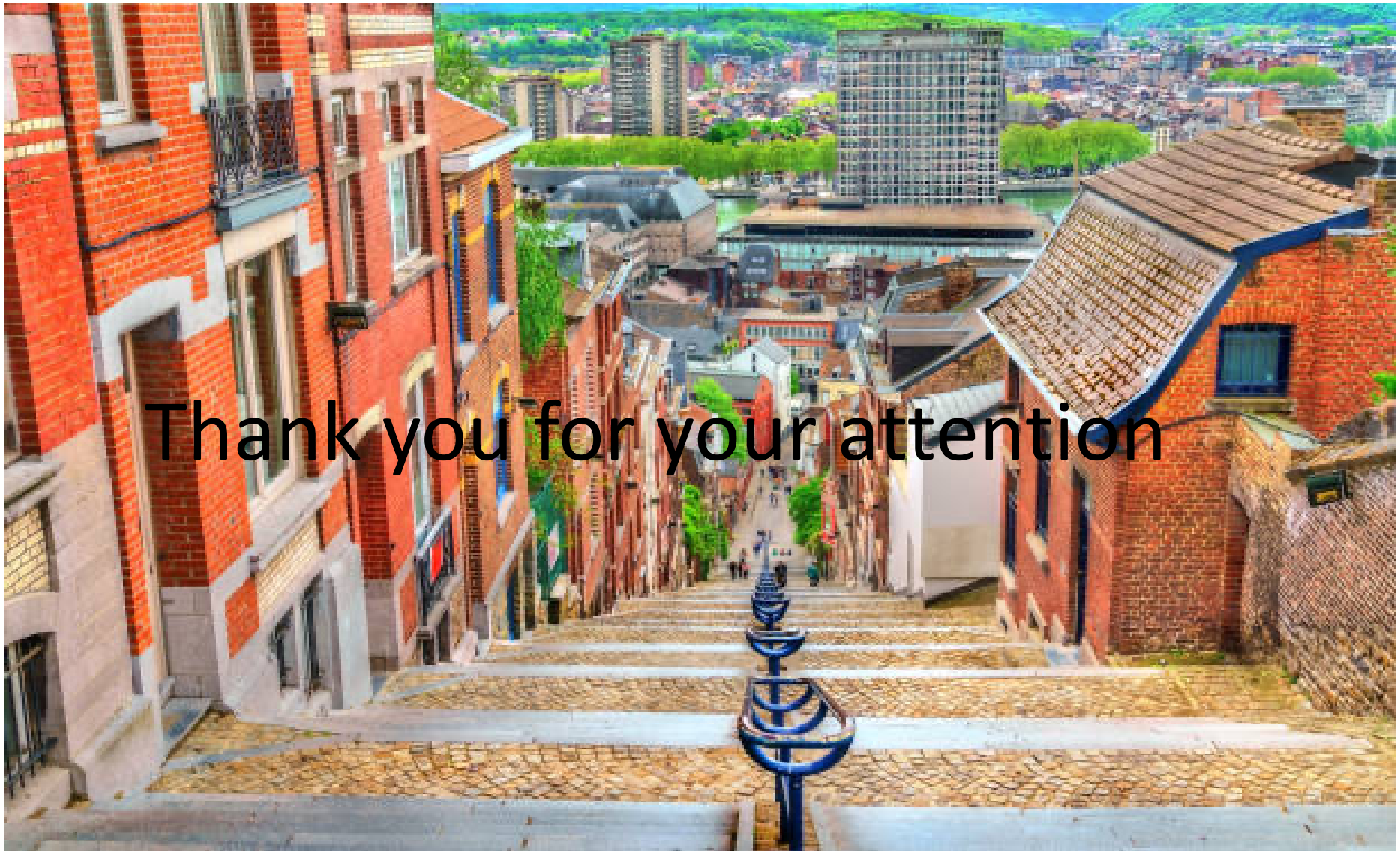
- Weaker humoral and cellular response than expected to an antigenic stimulus
- Association between immune paresis and antimetabolites (MM)
- Selective prophylactic administration of monoclonal antibodies?

Conclusion

- HTR are at high risk of morbidity and mortality from COVID-19 compared to the general population

- Outcomes are improving compared to the early phase of the pandemic (management strategies, better knowledge of the disease)

- Challenges remain regarding the timing of the vaccination and appropriate adjustement in immunosuppression


Thank you for your attention

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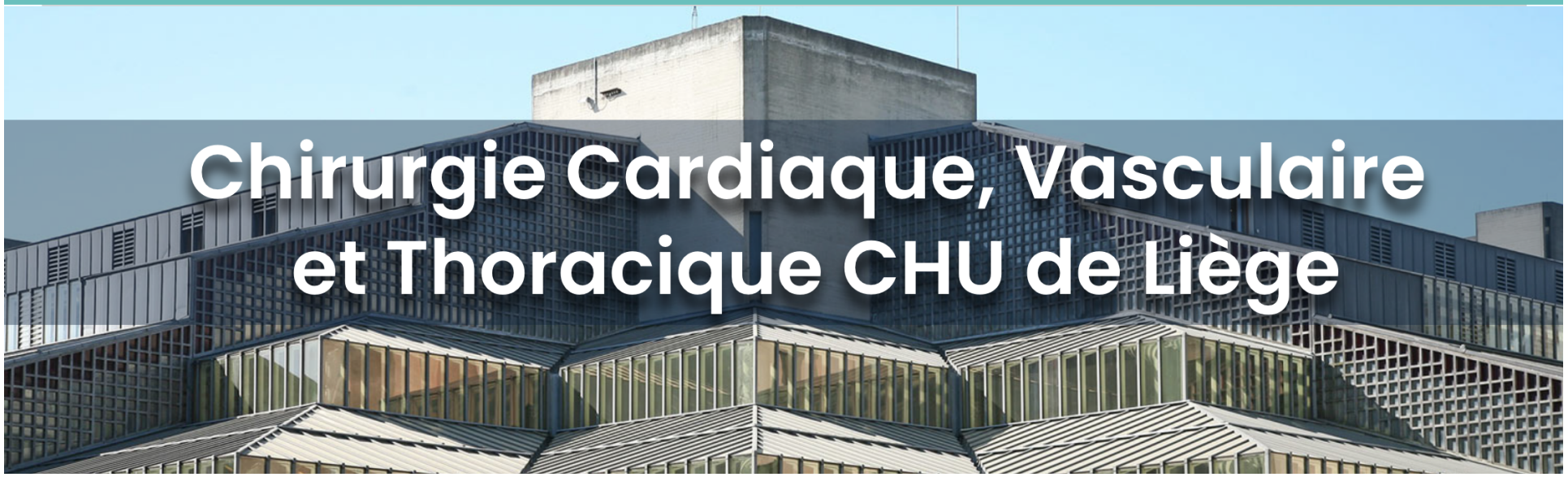
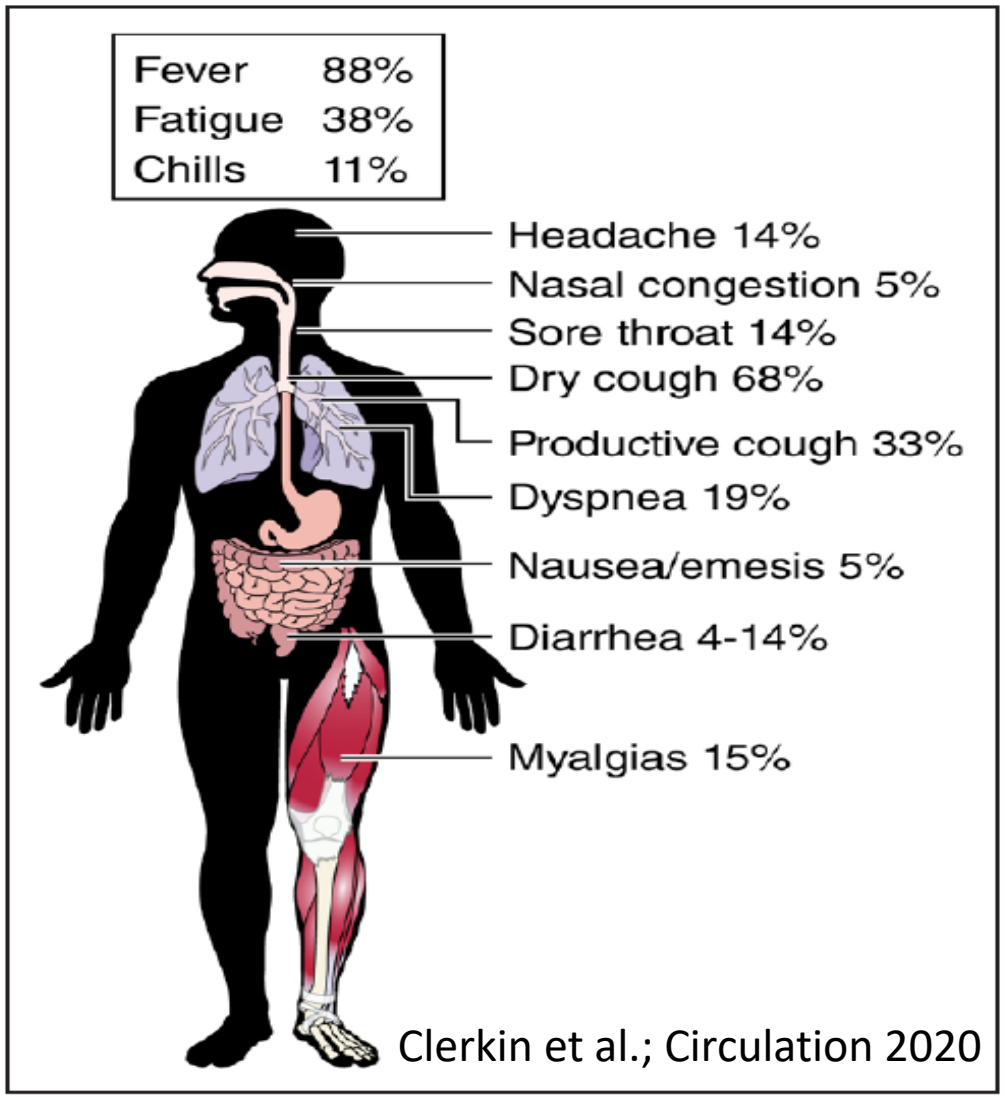
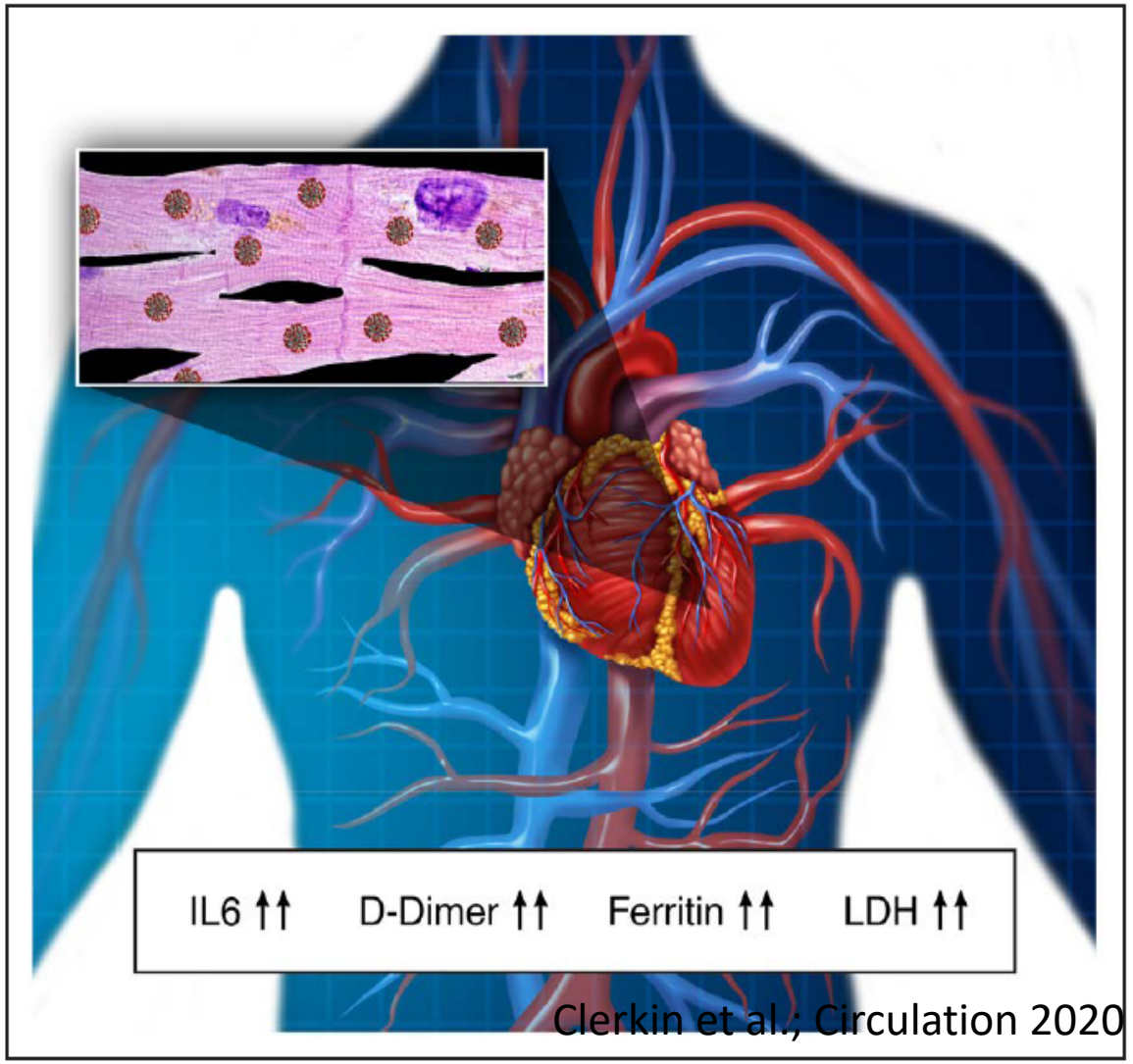
ACCUEIL





Clerkin et al.; Circulation 2020



Clerkin et al.; Circulation 2020

SARS-CoV-2 in Solid Organ Transplant Recipients: A Structured Review of 2020

Markus Quante[a], Linda Brake[a], Alexander Tolios[b,c,d], Andrea Della Penna[a], Christoph Steidle[a], Magdalena Gruendl[e], Anna Grishina[f], Helene Haeberle[g], Martina Guthoff[h,i,j], Stefan G. Tullius[k], Alfred Königsrainer[a,l], Silvio Nadalin[a], and Markus W. Löffler[a,l,m,n*]

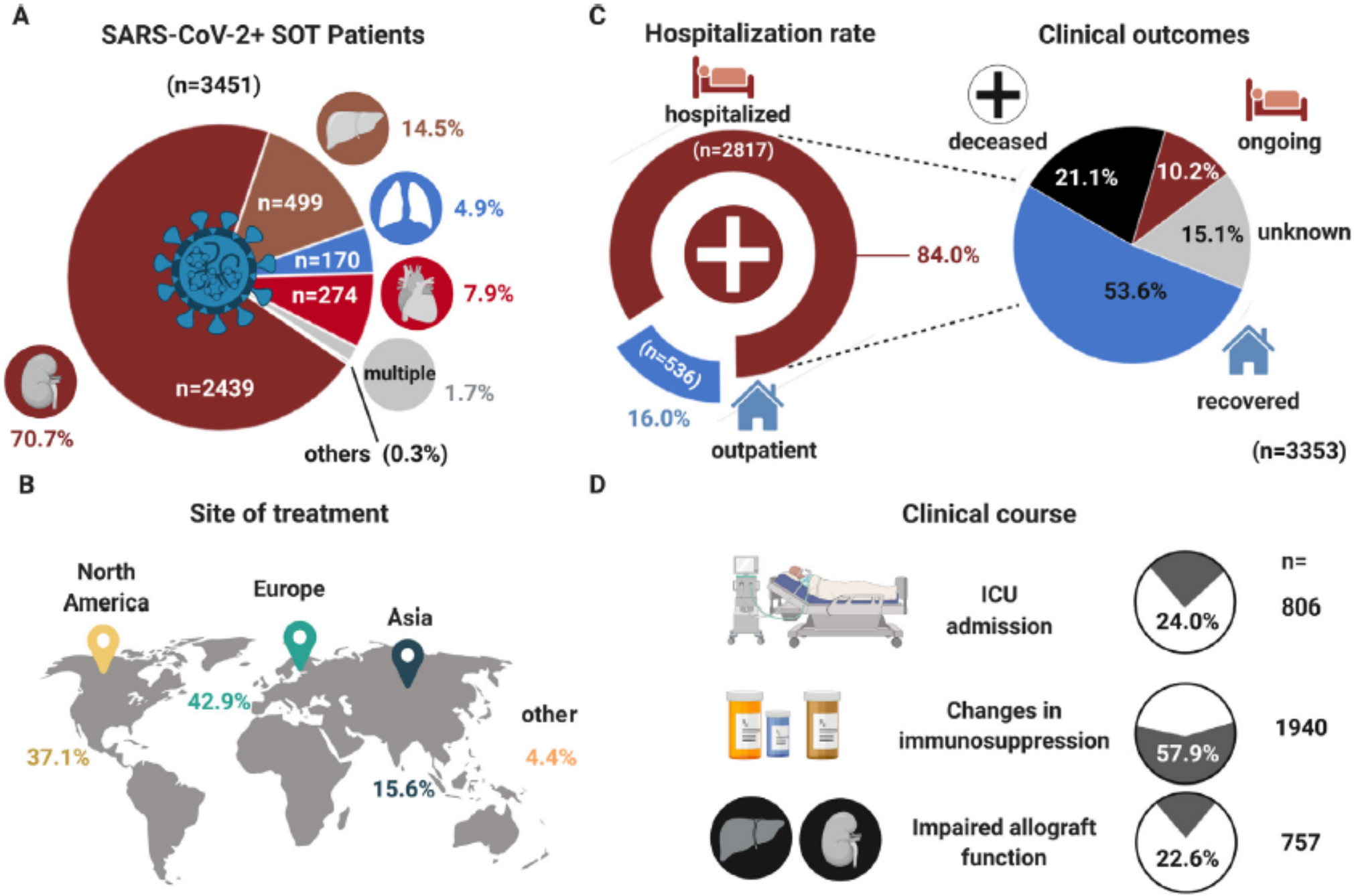
Background. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is challenging health systems all over the world. Particularly high-risk groups show considerable mortality rates after infection. In 2020, a huge number of case reports, case series, and consecutively various systematic reviews have been published reporting on morbidity and mortality risk connected with SARS-CoV-2 in solid organ transplant (SOT) recipients. However, this vast array of publications resulted in an increasing complexity of the field, overwhelming even for the expert reader.

Methods. We performed a structured literature review comprising electronic databases, transplant journals, and literature from previous systematic reviews covering the entire year 2020. From 164 included articles, we identified 3451 cases of SARS-CoV-2–infected SOT recipients.

Results. Infections resulted in a hospitalization rate of 84% and 24% intensive care unit admissions in the included patients. Whereas 53.6% of patients were reported to have recovered, cross-sectional overall mortality reported after coronavirus disease 2019 (COVID-19) was at 21.1%. Synoptic data concerning immunosuppressive medication attested to the reduction or withdrawal of antimetabolites (81.9%) and calcineurin inhibitors (48.9%) as a frequent adjustment. In contrast, steroids were reported to be increased in 46.8% of SOT recipients.

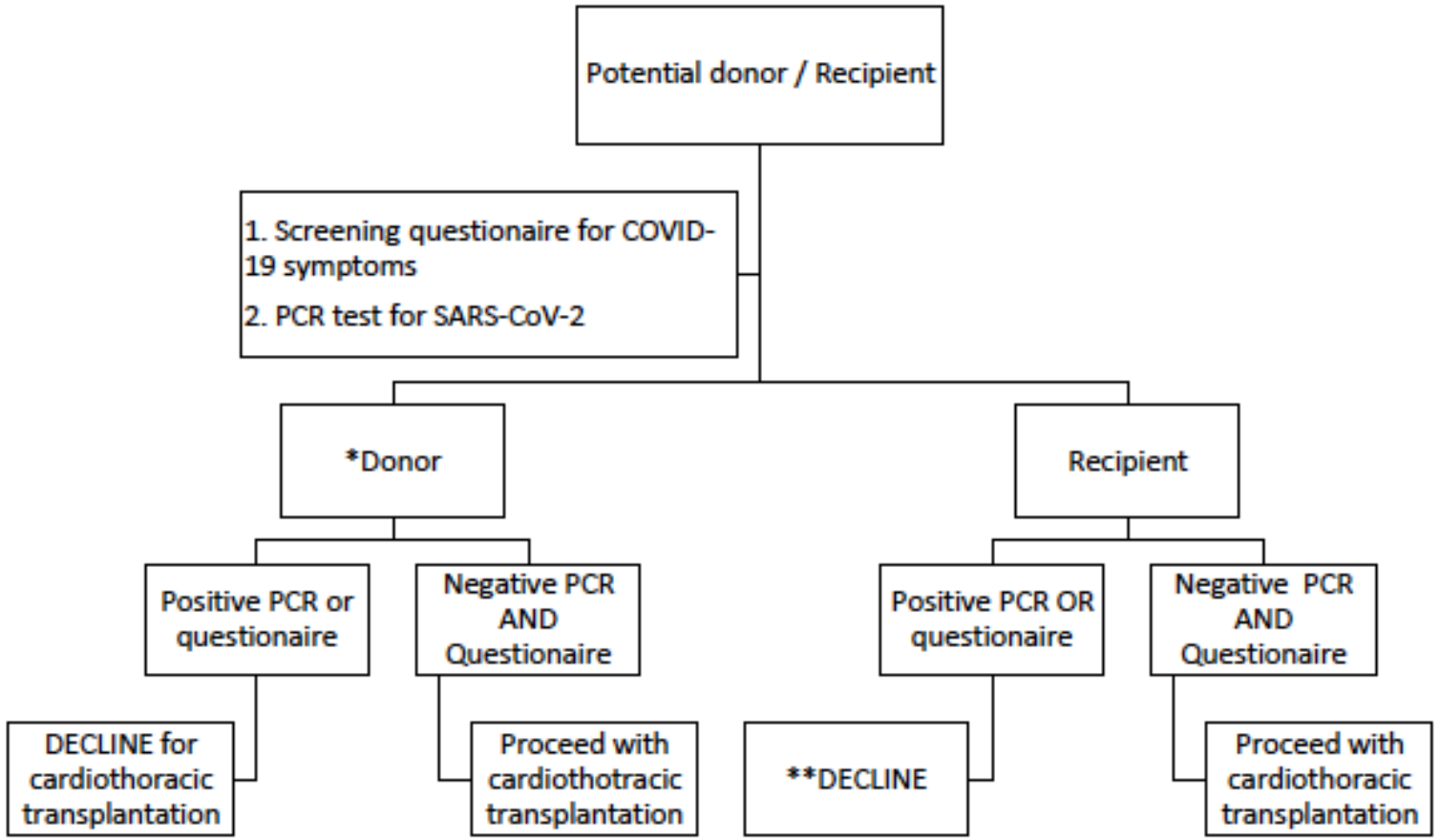
Conclusions. COVID-19 in SOT recipients is associated with high morbidity and mortality worldwide. Conforming with current guidelines, modifications of immunosuppressive therapies mostly comprised a reduction or withdrawal of antimetabolites and calcineurin inhibitors, while frequently maintaining or even increasing steroids. Here, we provide an accessible overview to the topic and synoptic estimates of expectable outcomes regarding in-hospital mortality of SOT recipients with COVID-19.

Quante M, Transplantation Proceedings 2021



Quante M, Transplantation proceedings 2021

Figure 1. Screening pathway for donor and recipient screening at time of organ offer.

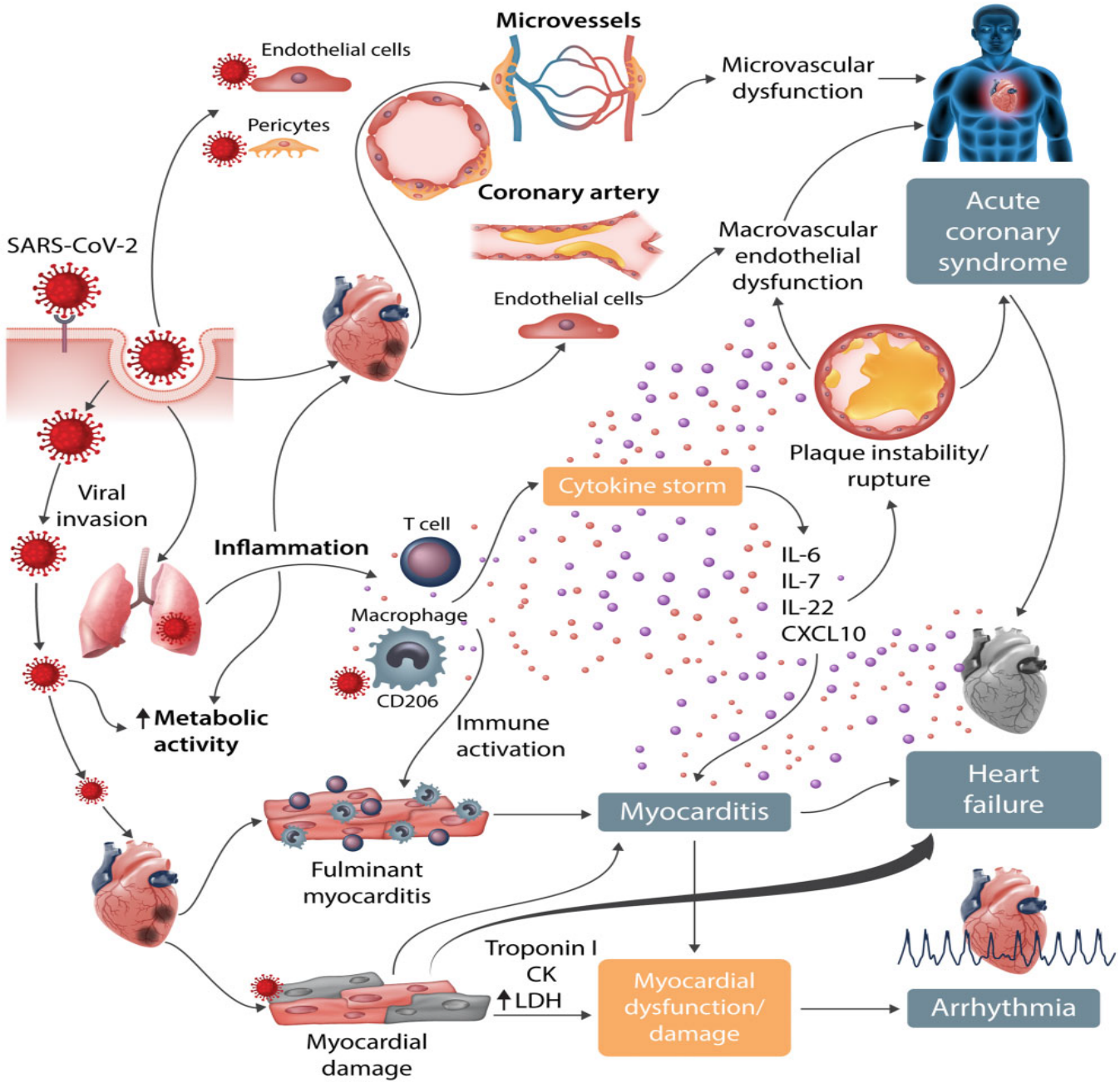


*consider CT chest for donor and decline if concerning for COVID-19

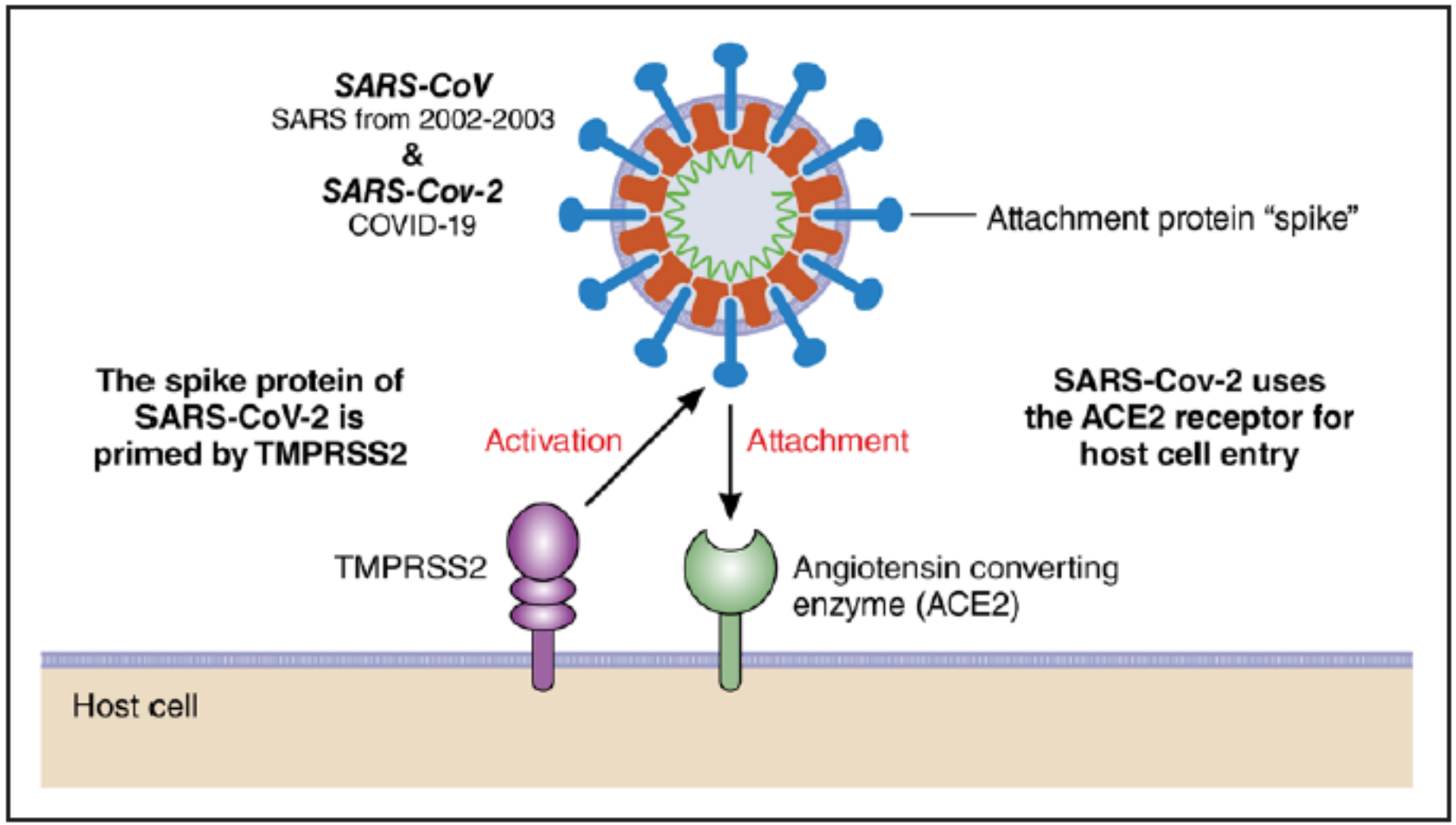
** Exceptions can be made on a case-by-case basis as noted in Table 2

- Recommend deep respiratory sample in lung donor for SARS-CoV-2 testing
- N-95 mask or equivalent plus face shield in operating room for lung transplant
- Current data does not suggest a change in induction or maintenance immunosuppression

ISHLT Guidelines 2021



Guzik T; cardiovascular research 2020



Clerkin et al.; Circulation 2020