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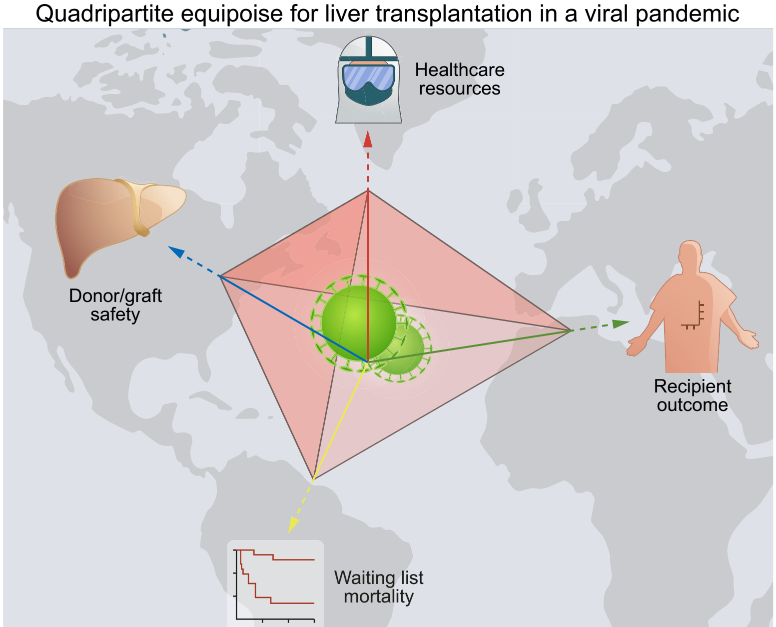
An international multicenter study of protocols for liver transplantation during a pandemic: A case for quadripartite equipoise

Graphical abstract

Quadripartite equipoise for liver transplantation in a viral pandemic



Highlights

- COVID-19 outbreak has increased operational burden on healthcare systems worldwide.
- Frameworks to balance need for liver transplant against limited resources needed.
- International multicenter study of policies for transplant prioritization conducted.
- Novel four-dimensional model of quadripartite equipoise to balance ethical tensions.
- Fluctuation of model over time guides need to pursue or limit transplant activity.

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Lay summary

There is an urgent need for ethical frameworks to balance the need for liver transplantation against the availability of national resources during the COVID-19 pandemic. We describe a four-dimensional model of quadripartite equipoise that models these ethical tensions and can guide the regulation of transplant activity in response to the increasing burden on healthcare systems.

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An international multicenter study of protocols for liver transplantation during a pandemic: A case for quadripartite equipoise

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Background & Aims: The outbreak of COVID-19 has vastly increased the operational burden on healthcare systems worldwide. For patients with end-stage liver failure, liver transplantation is the only option. However, the strain on intensive care facilities caused by the pandemic is a major concern. There is an urgent need for ethical frameworks to balance the need for liver transplantation against the availability of national resources.

Methods: We performed an international multicenter study of transplant centers to understand the evolution of policies for transplant prioritization in response to the pandemic in March 2020. To describe the ethical tension arising in this setting, we propose a novel ethical framework, the quadripartite equipoise (QE) score, that is applicable to liver transplantation in the context of limited national resources.

Results: Seventeen large- and medium-sized liver transplant centers from 12 countries across 4 continents participated. Ten centers opted to limit transplant activity in response to the pandemic, favoring a "sickest-first" approach. Conversely, some larger centers opted to continue routine transplant activity in order to balance waiting list mortality. To model these and other ethical tensions, we computed a QE score using 4 factors – recipient outcome, donor/graft safety, waiting list mortality and healthcare resources – for 7 countries. The fluctuation of the QE score over time accurately reflects the dynamic changes in the ethical tensions surrounding transplant activity in a pandemic.

Conclusions: This four-dimensional model of quadripartite equipoise addresses the ethical tensions in the current pandemic. It serves as a universally applicable framework to guide regulation of transplant activity in response to the increasing burden on healthcare systems.

Lay summary: There is an urgent need for ethical frameworks to balance the need for liver transplantation against the availability of national resources during the COVID-19 pandemic. We describe a four-dimensional model of quadripartite equipoise that models these ethical tensions and can guide the regulation of transplant activity in response to the increasing burden on healthcare systems.

Introduction

In December 2019, a cluster of patients developed pneumonia of unknown cause that was linked to a seafood wholesale market in Wuhan, China.[1] Since then, severe acute respiratory syndrome coronavirus 2 – which causes COVID-19 – has spread rapidly across the world, leading the World Health Organization (WHO) to declare a global pandemic on 11 March 2020. The surge in the number of people seeking medical treatment has temporarily overwhelmed health services, leading to concerns regarding the allocation of scarce resources such as intensive care facilities.[2,3]

This has immediate implications on liver transplantation worldwide. The availability of intensive care facilities is crucial, not only for the identification of donors for deceased donor transplantation, but also for the care of post-operative patients.[4] In such austere times, a balance must be achieved between the survival benefit of transplantation, waiting list mortality, risk to donors and diminishing national resources. The availability of viral testing for patients as well as healthcare workers also remains a major concern.

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The aim of this study was to perform an international multicenter analysis to understand the evolution in response of major transplant centers from the initial outbreak to the declaration of a pandemic. We propose a model of quadripartite equipoise to guide ethical decision-making in the context of liver transplantation during a viral pandemic.

Materials and methods

Epidemiology

The incidence of COVID-19 cases in participating countries was obtained from the WHO situation reports from 15 February to 31 March 2020, to encompass the study period.[5] The disease burden per capita was measured as the number of cases per 100,000 of population.[6]

International multicenter survey: Study design

This study was conducted using an open, voluntary, internet-based survey designed in accordance with the 'Checklist for Reporting Results of Internet E-Surveys (CHERRIES) framework'.[7] The survey was created and disseminated through a structured communication network involving electronic mailing lists through an academic account held by the National University Hospital System, Singapore. Informed consent was obtained for participation in this study and no incentives were offered to the participants. The survey was sent to senior (more than 5 years of experience) transplant surgeons involved in organ allocation at transplant centers across Asia, Europe, North and South America. 'Transplant centers' were defined as any hospital with a liver transplant program that has been approved by their local regulatory authorities. Centers were chosen from countries that were experiencing different phases of the pandemic. At the time of study design, Hong Kong, South Korea, Taiwan and Singapore had achieved a 'flattening of the curve', the US, UK, Spain, Italy, and Germany were on an upward trajectory, and India, Chile and Argentina were in the early phases of local transmission.

The questionnaire was designed by authors CC/IS/GB using Google Forms (Mountain View, CA, USA) and sent via secure link on email. Responses were collected between 15 – 22 March 2020. All relevant information about the questionnaire and the study was provided to the participants prior to starting, and participants were able to withdraw from the analysis at any point.

International multicenter survey: Questionnaire design

A 41-item self-administered online questionnaire was created and sub-divided into 4 sections: (i) center demographics; changes in transplant activity and viral screening protocols following the (ii) initial outbreak (January 2020) and (iii) WHO declaration of viral pandemic (11 March 2020); (iv) suggested protocol changes given their local context at time of reporting.

A further survey was undertaken from 22 – 25 March 2020 for Hong Kong, Singapore, South Korea, the US, Germany, the UK and Italy. Data was requested for detailed protocols describing (i) the recruitment of donors and prioritization of recipients; (ii) viral screening; and (iii) precautions for healthcare workers involved in transplantation.

Quadripartite equipoise score

Following the international survey, the authors C.C. and G.B. constructed the model of quadripartite equipoise, a conceptual ethical framework intended to address the ethical tension arising from the need for liver transplantation within a pandemic. It was then circulated and discussed amongst all authors and a consensus was reached for this framework. It was subsequently tested on various countries using multiple timepoints throughout the pandemic, the results of which were once again shared with all authors for feedback. The final model was agreed upon by all authors. The model consists of the following factors:

- *Recipient outcome* was defined using the national 5-year overall survival following liver transplantation of both adult living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) recipients.
- *Donor/graft safety* was described using the risk of morbidity or mortality of surgery to living donors in LDLT, and the risk associated with the use of marginal or extended criteria donors in DDLT. Due to varying practices of LDLT and DDLT across centers, this factor was fixed at a maximal value for this study.
- *Waiting list mortality* was used as a measure of the clinical need for liver transplantation and defined using the annual national waiting list mortality where the higher the waiting list mortality, the greater the need for transplantation. This was calculated as the percentage of patients on the waiting list removed due to death each year.
- *Healthcare resources* was used to quantify the operational burden placed on intensive care facilities by the viral pandemic. As such, healthcare resources were measured as the ratio of intensive care unit (ICU) beds to total number of active COVID-19 cases by country. The number of active cases is defined as the total number of confirmed cases minus recovered cases and deaths. The data was log-transformed using the minimum and maximum values obtained from all countries across all timepoints to increase granularity at the lower end of the scale, where ethical tension was highest.

The quadripartite equipoise score was derived using the volume of a triangular pyramid formed by the variation of the 4 factors. For example, a center with a 5-year survival of 100%, 0% LDLT donor risk, 100% annual waiting list mortality and 100% availability of intensive care facilities would have a maximum score of 1.000 on all 4 axes. The overall score reflects the need for transplantation balanced by these 4 factors. An increasing score supports the continuation of transplant activity despite the competing needs of the pandemic, while a decreasing score suggests a need to limit activity. The QE score was computed for 7 countries (Hong Kong, Singapore, South Korea, US, Germany, UK and Italy) on 1, 12 and 24 March 2020 to reflect the changes that took place surrounding the WHO declaration of the pandemic.

The triangular base of the pyramid was defined using recipient outcome, donor/graft safety and waiting list mortality. These were each drawn from the centroid to the 3 vertices of the triangle at an equal angle of 120°. The vertical axis was defined using the healthcare resources factor. Three-dimensional modelling of the pyramid was performed using Rhinoceros 3D (Version 6; Seattle, WA, USA). The volume of each pyramid was extracted using Grasshopper, a parametric modelling plug-in for Rhinoceros 3D. Data was obtained from public registries and published literature.[8–16] The 5-year overall survival and annual waiting list mortality for Singapore is currently unpublished and was obtained directly from the national registry.

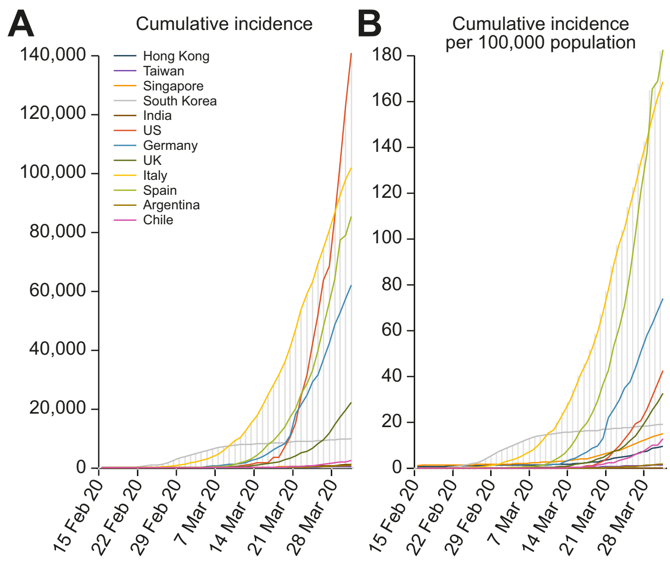

Fig. 1. Worldwide trends in the incidence of COVID-19. (A) Incidence of confirmed COVID-19 cases by country. (B) Cumulative incidence of confirmed COVID-19 cases per 100,000 population by country. (This figure appears in color on the web.)

Results

At the time of submission, the number of infections worldwide remains on an exponential trajectory (Fig. 1). It is in this context that we first aimed to survey the changes to prioritization in liver transplantation and the screening of donors and recipients for viral infections.

Seventeen large- and medium-sized liver transplant centers from 12 countries across 4 continents participated. The response rate of centers surveyed was 100%. Characteristics of the transplant activity of participating centers are shown in Table 1. Due to the low rates of deceased donation, there was a higher waiting list mortality of 10–20% in 6 out of 7 Asian centers where the proportion of LDLT performed was concordantly higher, encompassing over 20% of all transplants. While all centers had a criterion for the listing of super-urgent recipients, the criteria for medical urgency was less consistently defined and included acute or acute-on-chronic liver failure, arterial thrombosis, or model for end-stage liver disease (MELD) score of >29 (Table 1).

The changes in protocols for transplant activity between centers are shown in Fig. 2. At the initial outbreak, there was a continuation of standard transplant activity in all centers except in Singapore. Having had experience with the severe acute respiratory syndrome epidemic in 2003,[17,18] Singapore responded early by limiting transplant activity to medically urgent DDLT and LDLT, with the consideration of other transplants on a case-by-case basis.

In response to the declaration of viral pandemic by the WHO, 10 out of 17 centers limited their transplant activity. Hong Kong and South Korea had already experienced an initial surge in infections and opted to continue standard transplant activity. It is interesting to note that at that time, larger centers in the UK, US and Germany also maintained standard transplant activity despite the increasing number of COVID-19 cases. In contrast, despite the relatively low incidence of cases in South America, centers from both Argentina and Chile opted to limit transplant activity. The implementation of viral screening for donors and

Table 1. Overview of transplant activity at centers surveyed.

Country	Number of patients on waiting list	Mortality rate on waiting list	Number of transplants performed per year	LDLT % of total transplants performed	National criteria for super-urgent transplants	Center-specific criteria for medically urgent transplant
Singapore	<50	10–20%	<50	20–50%	Yes	ICU admission for grade 3–4 hepatic encephalopathy, ALF with MELD ≥25, ACLF
Hong Kong	50–100	10–20%	50–100	20–50%	Yes	n.a.
Taiwan	100–200	<10%	>100	>50%	Yes	ALF, ACLF
South Korea	100–200	10–20%	>100	>50%	Yes	n.a.
India (A)	50–100	10–20%	>100	>50%	Yes	n.a.
India (B)	<50	10–20%	<50	<20%	Yes	n.a.
India (C)	<50	10–20%	>100	>50%	Yes	n.a.
UK (A)	100–200	<10%	>100	<20%	Yes	ALF, Early graft failure
UK (B)	50–100	<10%	>100	<20%	Yes	n.a.
Italy (A)	<50	<10%	<50	<20%	Yes	n.a.
Italy (B)	<50	<10%	<50	<20%	Yes	MELD score >29
Spain	<50	10–20%	<50	<20%	Yes	ALF, ACLF, early graft failure
Germany	100–200	<10%	50–100	<20%	Yes	ACLF with ICU admission
US (A)	100–200	<10%	>100	20–50%	Yes	UNOS status 1 policy
US (B)	100–200	<10%	50–100	20–50%	Yes	UNOS status 1 policy
Chile	<50	<10%	<50	<20%	Yes	n.a.
Argentina	50–100	10–20%	50–100	<20%	Yes	MELD score

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; ICU, intensive care unit; MELD, model for end-stage liver disease; n.a, not applicable; UNOS, United Network for Organ Sharing.

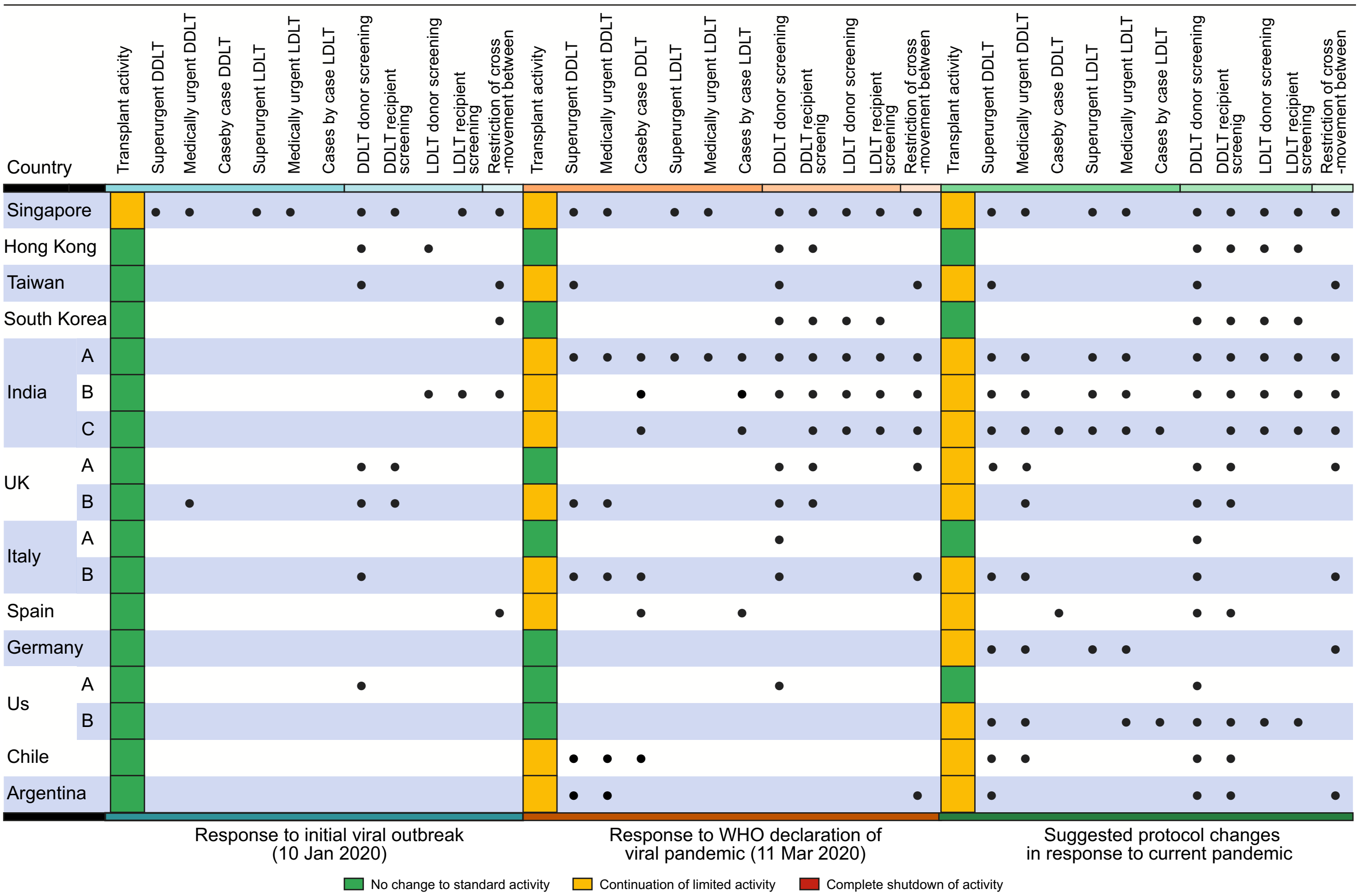

Fig. 2. Summary of responses from transplant centers describing changes in transplant activity in response to viral pandemic and suggestions for change. Responses are tabulated based on response to initial outbreak (left), WHO declaration of pandemic (middle) and suggested protocols (right). Green, amber and red boxes are used to describe the changes in prioritization of transplant activity. DDLT, deceased donor liver transplantation; LDLT, living donor living transplantation; WHO, World Health Organization. (This figure appears in color on the web.)

recipients varied widely. Several Asian centers mandated screening of all donors and recipients, whereas screening in Western centers was mostly limited to deceased donors at the time of the survey.

When queried on "suggested protocols" for their institution, most respondents opted to limit transplant activity and favored a "sickest-first" approach (Fig. 2), with the allowance of other transplants on a case-by-case basis. Nearly all respondents felt that the screening of donors and recipients for COVID-19 prior to transplantation was indicated.

A detailed review of the changes in response to the pandemic was requested from 7 major transplant centers (Table 2). While donor assessment was largely unchanged, there was a decrease in referrals for deceased donors in the US and Italy. In the UK, the use of marginal grafts was reduced to minimize strain on ICUs from post-transplant care. Contact and travel history screening was actively performed but the former was challenging in the US due to limited testing capacity during the study timeframe. COVID-19 testing was mandatory for both donors and recipients in Singapore, South Korea and Germany. Donors were also excluded on clinical suspicion of respiratory compromise or positive contact history.

Free movement of organ procurement teams continued in all centers. While the US has the largest land space requiring regular fly-out retrievals, at the point of submission, there was a lack of consistency between centers on restrictions to this activity. In all centers, standard personal protective equipment was used and protective measures for donor coordinators were implemented.

Based on the results of the survey, the patterns of transplant activity did not appear to correspond with the burden of COVID-19 on healthcare resources, highlighting a clear need for a framework to guide the prioritization of transplant activity. Therefore, we modelled the ethical tension that arises when considering liver transplantation during a viral pandemic, to derive a quadripartite equipoise score for 7 countries as shown in Fig. 3.

The shape and size of the triangular base characterizes the transplant activity of each country. As previously described, donor/graft safety was fixed at a maximal value of 1.000. Differences in the triangular base between countries were determined by the variation of recipient outcome (5-year recipient survival, 71.3% to 85.7%) and waiting list mortality (5.1% to 34.5%). The vertical axis indicating the availability of healthcare resources decreased over time in most centers, reflecting the exponential increase in cases worldwide. In South Korea, this increased following an initial decrease, demonstrating the country's successful attempt to 'flatten the curve' (Fig. 3).

Table 2. Comparison of detailed protocol changes in response to increasing national viral disease burden.

	Hong Kong	Singapore	South Korea	US	Germany	UK	Italy
Process for recruitment of deceased donors	Unchanged recruitment by donor coordinators and case managers in ICUs	Unchanged recruitment by donor coordinators and case managers in ICUs	Unchanged recruitment by donor coordinators and case managers in ICUs	Largely unchanged although lack of ventilators and ICU beds has caused donor numbers to decrease significantly	Unchanged recruitment by donor coordinators and case managers in ICUs	Reduction of age of donors to <60 for DBD, and <50 DCD	Unchanged recruitment by donor coordinators and case managers in ICUs
Process for recruitment and pairing for living donor transplantation	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
Acceptance and prioritization of recipients	No change to standard indications for LDLT	Transplants only performed for urgent LDLT for acute liver failure or acute-on-chronic liver failure	No change to standard indications for LDLT	Transplant only performed for high MELD, acute liver failure and UNOS Status 1 patients	Continuation of DDLT and LDLT on a case-to-case basis by individual transplant centers	No change to standard indications, however some centers have deferred activity	No change to standard indications for DDLT
Travel history screening*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Contact history screening**	Yes	Yes	Yes	± (difficult as testing is not widespread)	Yes	Yes	Yes
Clinical evaluation	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory infections	Examination of donor and recipient for clinical signs or symptoms or acute/severe respiratory infections Urgent CT thorax for donor and recipient	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory infections	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory infections	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory tract infections	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory infections	Examination of donor and recipient for clinical signs or symptoms of acute/severe respiratory infections
COVID-19 qRT-PCR testing	For suspected COVID-19 cases and those with recent travel to high risk areas	For deceased donors: 2 separate tests For living donors: 3 separate tests	For any suspected COVID-19 cases: 2 separate tests For deceased donors: 2 separate tests	For all donors and ideally all recipients however limited by availability of testing	For deceased donors: 1 mandatory test (to repeat if taken >48 h prior to donation) For living donors: optional unless suspected COVID-19 cases For all recipients: optional unless suspected COVID-19 cases	For all deceased donors	For deceased donors: 2 separate tests For all recipients: in the presence of symptoms or when there is clinical suspicion of infection due to close contact with suspected or confirmed cases of COVID-19
Exclusion criteria	Living donors with positive COVID-19 test Deceased donors with positive COVID-19 test or fever or unknown origin	Suspected or confirmed cases of COVID-19 History of travel to mainland China within the last 28 days Donors with respiratory symptoms without a positive COVID-19 qRT-PCR test	Suspected or confirmed cases of COVID-19 History of contact with confirmed cases of COVID-19 within the last 14 days	Confirmed COVID-19 donors Suspected or confirmed COVID-19 recipients	Suspected or confirmed cases of COVID-19 (Clearance for LDLT can be obtained by repetitive negative COVID-19 PCR testing during quarantine period of 14 days) Suspension of organ donation in high-risk areas as stated by the national public health institute	Suspected or confirmed cases of COVID-19 History of contact with confirmed cases of COVID-19 within the last 14 days	Suspected or confirmed cases of COVID-19

(continued on next page)

Table 2. (*continued*)

	Hong Kong	Singapore	South Korea	US	Germany	UK	Italy
Movement between hospitals for organ procurement	Unchanged	Unchanged	Unchanged	Restriction of flyouts in discussion – 2 DDLTs performed with organ procurement performed at local and regional centers Some centers have not stopped flyouts	Unchanged Retrieval team members with suspected or confirmed COVID-19 are prohibited	Unchanged, continuation of national retrieval service	Retrieval team has to self-certify the following - No symptoms - No quarantine - Not awaiting swab result
Use of personal protection equipment	Standard surgical PPE	Standard surgical PPE	Standard surgical PPE	Standard surgical PPE	Standard surgical PPE	Standard surgical PPE	Standard surgical PPE
Specific precautions for donor coordinators	Suspension of all daily inspection in all hospitals to avoid transmission of infection from hospitals to hospitals, or from wards to wards. To undertake their duties only when they are alerted by ICU or neurosurgical staff about brain-dead donors	Split-team working Maintenance of a distance of >2 m when communicating Strict adherence to PPE in ICU Avoidance of COVID-19 isolation and observation wards	Deceased donors cannot be recruited from hospitals with COVID-19 patients Strict adherence to the level of protection when entering different areas of donation hospital	Unclear at present	Remote contact should be made where possible SNOD will obtain information about COVID-19 cases in the donor hospital Avoidance of COVID-19 isolation and observation wards Maintenance of a distance of >2 m when communicating	Screening of all donors medical /clinical to exclude any risk cases prior to donation nurse attendance	Strict adherence to local protection protocol for healthcare workers (standard PPE) Avoidance of department and ICU dedicated to COVID-19 Maintenance of a distance of >1.5 m when communicating

Results collated from 22–25 March 2020 from centers in Hong Kong, Singapore, South Korea, the US, Germany, and the UK.

DBD, donation after brain death; DCD, donation after cardiac death; ICU, intensive care unit; LDLT, living donor liver transplantation; PPE, personal protective equipment; qRT-PCR, real-time reverse transcription PCR.

*Includes screening donor and recipient for recent travel history to high-risk countries where the list was progressively expanded as the pandemic evolved.

**Includes the following: (i) anyone suspected or confirmed to have COVID-19, or have recently travelled to China or other countries of interest since December 2019; (ii) anyone with household members who have been suspected or confirmed to have COVID-19, or have recently travelled to China or other countries of interest since December 2019; and (iii) healthcare providers who have been involved in the care of patients with COVID-19 or any suspected cases in the last 28 days.

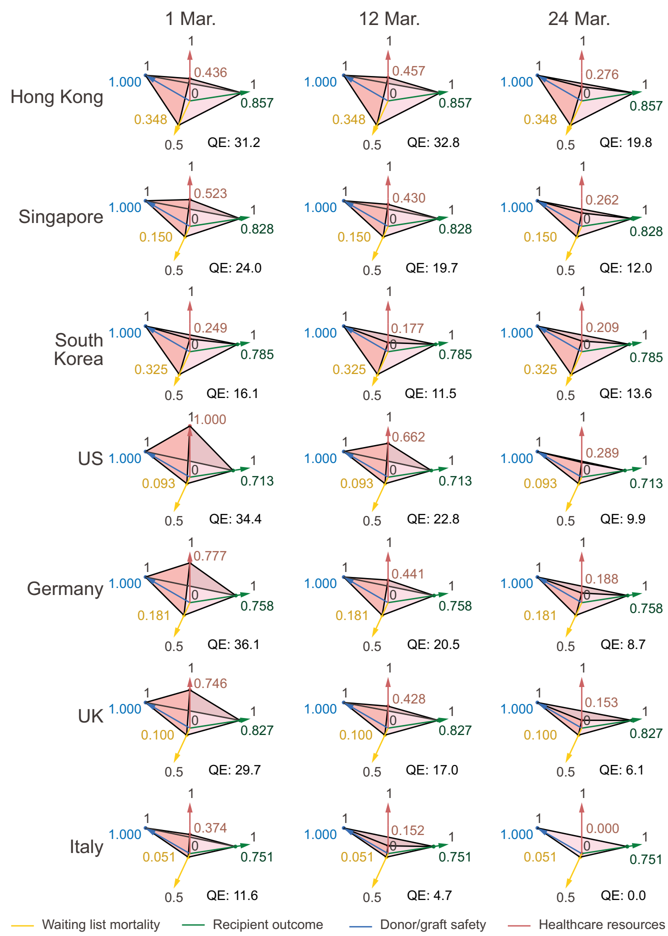

Fig. 3. Quadripartite equipoise of ethical considerations in liver transplantation during a viral pandemic. The quadripartite equipoise score is determined by the volume of the triangular pyramid generated by the variation in recipient outcome (green), donor/graft safety (blue), waiting list mortality (yellow) and healthcare resources (red). While the absolute value of the score remains arbitrary, the expansion or contraction of the model reflects the need to either pursue or limit transplant activity. (This figure appears in color on the web.)

While the healthcare resource axis between Hong Kong and the US was similar on 24 March (red; 0.276 *vs.* 0.289), the overall quadripartite equipoise score of Hong Kong was 19.8 compared to 9.9 for the US. The lesser degree of ethical tension estimated by the model favors the continuation of activity in Hong Kong relative to the US. The contraction of all pyramids over time, with a resultant decrease in quadripartite equipoise score, suggests a global need to decrease transplant activity (Fig. 3), albeit to varying degrees.

The quadripartite equipoise score of Italy on 1 March was 11.6, which was smaller than the score of several countries later into the pandemic. This was contributed to by both fewer ICU beds and the relatively low waiting list mortality of 5.1%. Respondents from Italy also reported a decrease in referrals for cadaveric donors, likely a reflection of both social restriction measures as well as an overwhelmed healthcare system. The computed quadripartite equipoise score on 24 March for Italy was 0.0.

Discussion

Since the outbreak of COVID-19 in January 2020, healthcare systems worldwide have been overwhelmed by rising numbers of infected patients.[19] It is no longer an option but rather a priority to set consistent ethical frameworks to manage this burden on our healthcare systems. In a pandemic, maximizing societal benefit is a necessary approach towards managing scarce resources such as intensive care facilities.[20] However, the democratization of these resources for lifesaving procedures such as organ transplantation adds a further layer of complexity. Unlike other organs with potential alternative or bridging therapies, liver transplantation is the only option for patients with end-stage liver failure.

To our knowledge, this is the largest study to date to catalogue the changes in the prioritization of transplant activity and viral screening in response to the COVID-19 outbreak. In response to the declaration of the pandemic, 10 out of 17 centers worldwide reduced their transplant activity by employing a "sickest-first" approach. Paradoxically, the transplantation of such patients may intensify the burden on ICUs and compromise access for COVID-19 patients with severe respiratory compromise,[21] thereby reducing the overall societal benefit. Of the 7 centers that transplant less than 50 livers a year, only 1 center did not reduce their transplant activity, while of those transplanting over 100 livers a year, 4 out of 6 also opted not to do so. On first glance this may reflect greater accessibility to resources in bigger centers (Fig. 2), however, this was not supported by the number of ICU beds per capita in their respective countries.[15,16]

Upon surveying respondents for their "suggested" response to the pandemic, nearly all respondents called for viral screening of both donors and recipients (Fig. 2). The transplant community has quickly initiated guidelines for viral testing and assessing transmission risks for patients as well as healthcare workers involved in transplantation.[22,23] However, access to testing varies widely, with South Korea testing asymptomatic individuals while, at the time of this study, the USA and UK were reserving testing only for high-risk patients. Globally, countries are now moving towards increasing their testing capacity.

Worldwide, organ allocation by MELD score or the "sickest-first" approach is modelled on the principle of justice, where fairness is determined by urgency.[24] However, other scores that consider the impact of donor factors draw on the principle of utility, which prioritizes maximizing the overall survival benefit from transplantation.[25,26] This illustrates the first 2 ethical dimensions of our model of quadripartite equipoise – recipient outcome and donor/graft safety. In LDLT, the ethical balance of donor safety juxtaposed against the survival benefit of the recipient has previously been termed "double equipoise".[27] In DDLT, graft safety refers to the risk conferred to the recipient by the quality of the cadaveric graft.[28] For instance, centers with higher usage of marginal cadaveric grafts would potentially lower both their recipient outcome and donor/graft safety axes but improve waiting list mortality. A limitation of this study is the fixed donor/graft safety score for all countries. This was done in view of the variation in practice regarding the types of donors or grafts used between centers, but sets an important framework that can be further modified based on local or national practices.

The third ethical dimension in the model is the clinical need as estimated by the waiting list mortality axis. The difference in waiting list mortality between Hong Kong (35.4%) and Italy (5.1%) reflects the difference in cadaveric organ supply in Asian and Western countries.[29,30] It highlights the intersection of clinical need with the first 2 dimensions, where in Hong Kong for example, the comparative shortage of cadaveric organs would support the need for LDLT despite accrual of risk by the donor. This has previously been described as a “tripartite equipoise”,[31] where the ethical tension arises from the shortage in the supply of organs. While the recipient outcome and waiting list mortality are unlikely to change within the short study period, the donor/graft safety axis can be modulated by accepting marginal grafts or living donors.

The final dimension of quadripartite equipoise is defined by the healthcare resources axis. This measures the operational burden of COVID-19 infections on the healthcare system and is estimated by the ratio of ICU beds to active COVID-19 cases per country. We acknowledge that using the number of active cases to measure the operational burden of the pandemic on the healthcare systems may overestimate the burden in countries that implement widespread testing, and underestimate the burden in countries with more conservative testing practices. Using the number of hospitalized patients introduces a similar degree of uncertainty as countries have different thresholds for hospital and ICU admissions. While the number of ICU admissions would likely most accurately reflect this burden, at the time of this submission, the national datasets of the absolute number of ICU admissions for the study period were unavailable.

However, a crucial point to note is that current best evidence suggests approximately 10% of patients with COVID-19 require intensive care.[32] The proportion of patients with active COVID-19 and respiratory compromise requiring ICU admission is a function of the viral pathology and is unlikely to vary significantly between countries. This effectively renders the burden on ICU facilities a relatively fixed fraction of the total number of active cases. It is with this in mind that the authors have chosen the most robust available data, the number of active cases by country, to estimate the burden on healthcare resources. As more data becomes available, this axis may be further refined to more accurately measure the operational burden caused by the pandemic.

The ethical tension between the burden of disease and need for transplantation arises from the shortage of resources, in particular the shared resource of ICU facilities. The Centers for Disease Control and Prevention has issued guidance for the allocation of ventilators in which they emphasize the need to apply “an ethical framework that focuses on saving as many lives as possible”.[33,34] While this affects policymakers, who decide on the supply of ventilators to hospitals, crucially it affects clinicians who are now pressed to make extremely difficult decisions to triage ventilators in ICUs.[35] In the context of the diminishing availability of such resources, the transplant community is faced with a similar dilemma in considering the prioritization of liver transplantation during a pandemic.

In our study, we modelled these 4 ethical considerations in a pyramidal structure and a quadripartite equipoise score was calculated using the volume of the model (Fig. 3). While the absolute value of the score remains nominal, the expansion or contraction of the model reflects the need to either pursue or limit transplant activity.

In South Korea, minimal variation in quadripartite equipoise score (16.1 to 13.6) (Fig. 3) was concordant with the continuation of standard activity described by the survey (Fig. 2). Singapore instituted early changes to decrease transplant activity and the need for this was indeed reflected in a steeper reduction in quadripartite equipoise score over time. At the point of manuscript submission, Italy continues to grapple with one of the highest numbers of COVID-19 cases per capita worldwide.[5] This surge in disease burden returned a quadripartite equipoise score of zero, reflecting the significantly reduced transplant activity reported by both respondents from Italy.

Initially, the US, UK, and Germany had the highest quadripartite equipoise scores, suggesting minimal ethical tension and thus supporting continued transplant activity (Fig. 2). However, all 3 countries subsequently saw a rapid contraction in quadripartite equipoise scores from an increased burden of COVID-19 on healthcare resources (Fig. 3). This calls for a decrease in transplant activity in order to achieve societal distributive justice – a view shared by 3 out of 5 respondents. We must remain cognizant that an overreaction to limit activity may increase waiting list mortality, while the continuation of activity at the expense of intensifying the strain on ICUs may increase COVID-19-related mortality. In future studies we hope to apply this model during the deceleration interval of the pandemic to analyze the effect of current changes in prioritization of transplant activity on waiting list mortality and the potential need to reinstate transplant activity.

While this model was derived using ethical considerations surrounding liver transplantation, the model is applicable to other life-saving organ transplantations by modifying the metrices used for each ethical dimension. For example, in organs where living donation is an option, the donor/graft safety score can be adjusted depending on the morbidity associated with the donor operation, which would be comparatively lower for kidney transplantation than for liver.[36,37] In the case of deceased donor transplantations, the axis can be calculated using organ-specific risk scoring systems that predict graft safety.[38,39] Recipient outcome and waiting list mortality can be similarly modified using organ-specific outcomes. However, unlike end-stage liver disease, other organs have potential bridging alternatives to transplantation – the left ventricular assist device for the heart, hemodialysis for kidneys and insulin supplementation for the pancreas. As such, a reduction in transplant activity may not affect the waiting list mortality as significantly as in liver transplantation. In addition, the degree of strain on ICU facilities will also vary depending on the organ-specific need for ICU support in the peri-operative period.

The contraction and expansion of this model of quadripartite equipoise can guide policymakers and transplant professionals to scale indications of transplantation, particularly when one axis evolves rapidly. With more countries achieving a ‘flattening of the curve’, the model may also guide the restarting of transplant activity. Local solutions to ethical problems that face individual transplant centers must be shared across borders to defeat this pandemic while minimizing societal losses. This model is an important aid in guiding transplant activity in these times, and will promote greater clarity, collaboration and support from within the international community.

Abbreviations

DDLT, deceased donor liver transplantation; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing; WHO, World Health Organization.

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Conflict of interest

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Authors' contributions

All authors contributed to data curation, formal analysis and manuscript review/editing. AW contributed to software and visualization. CC, IS, and GB contributed to conceptualization and methodology. CC and GB contributed to writing of the original draft.

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Supplementary data

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