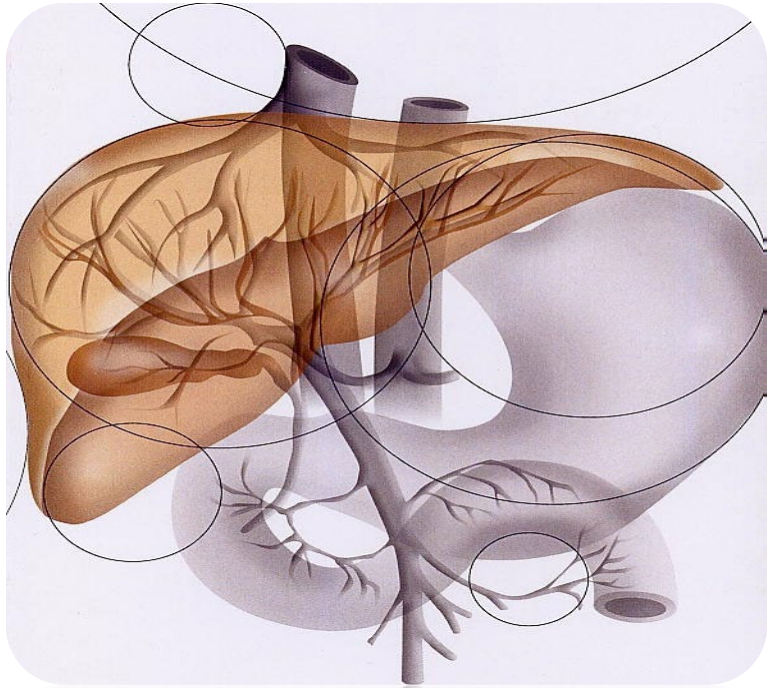
COVID-19 and liver transplantation



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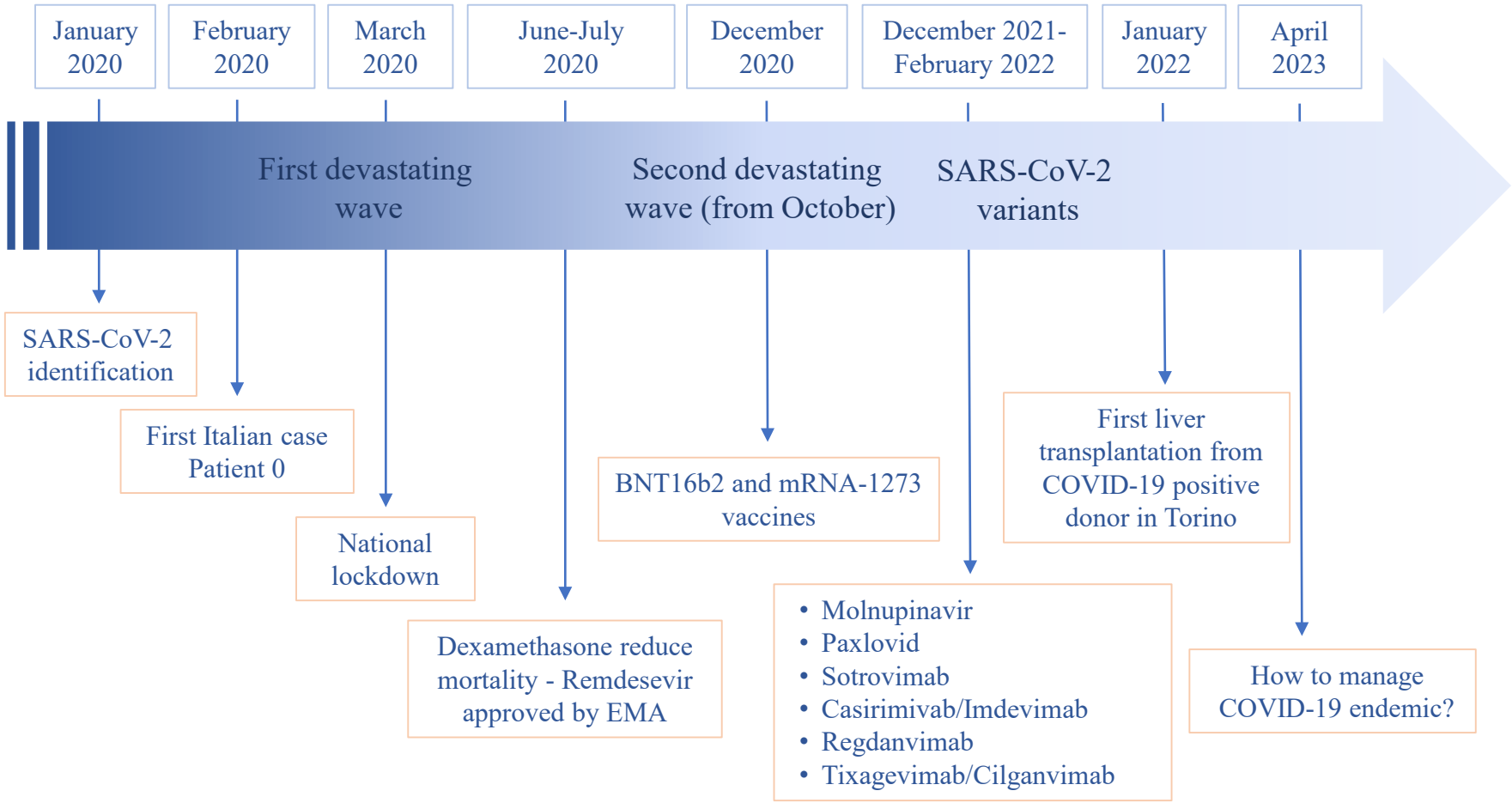
Highlights from the history of COVID-19



Agenda

- Impact of COVID-19 in liver transplant programs
- COVID-19 induced mortality in liver transplantated patients
- Prevention and management of COVID-19 in liver transplanted patients
  - Recipients and donors
- Open issues

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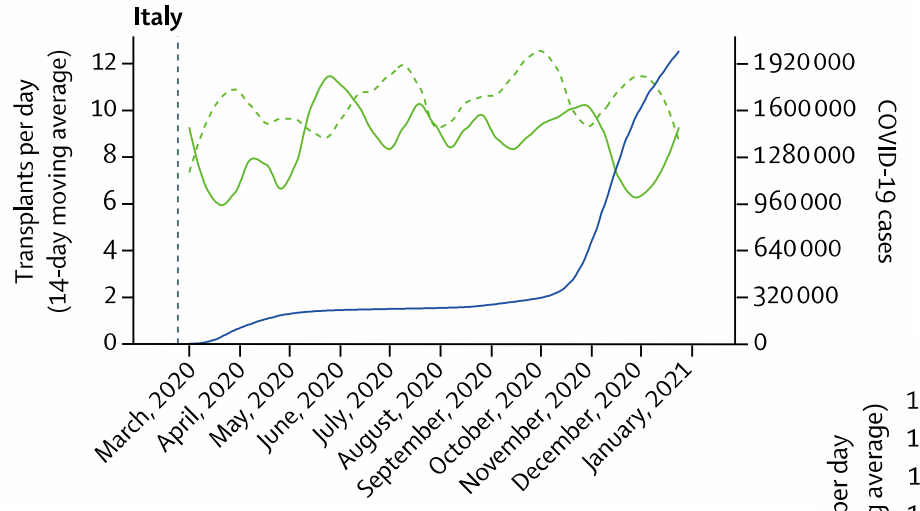
Change in overall observed solid organ transplant counts between 2020 from the date of the first 100 reported cumulative COVID-19 cases until the end of follow–up (Dec 2020)

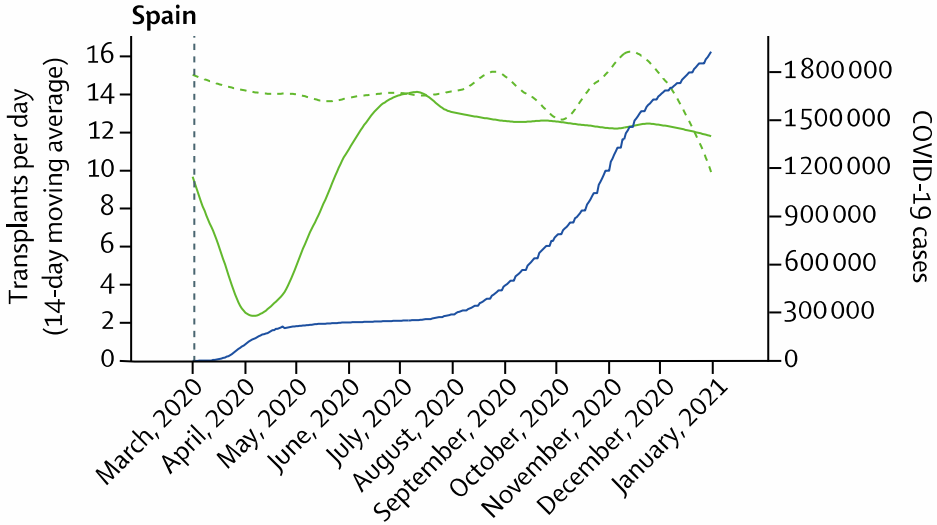
	Overall	Kidney	Liver	Lung	Heart
Argentina*	−564 (−60·91%)	−429 (−64·32%)	−107 (−56·61%)	−8 (−47·06%)	−20 (−37·74%)
Austria	−56 (−10·22%)	−53 (−17·91%)	6 (5·08%)	0	−9 (−16·36%)
Belgium	−166 (−22·46%)	−78 (−22·67%)	−49 (−20·68%)	−16 (−17·39%)	−23 (−34·85%)
Brazil	−2174 (−28·9%)	−1735 (−32·89%)	−307 (−16·51%)	−50 (−56·82%)	−82 (−27·42%)
Canada	−227 (−9·86%)	−229 (−16·29%)	5 (1·09%)	4 (1·47%)	−7 (−4·24%)
Chile*	−47 (−54·02%)	−23 (−46·94%)	−10 (−45·45%)	−6 (−85·71%)	−8 (−88·89%)
Croatia	−85 (−37·28%)	−35 (−36·84%)	−34 (−33·01%)	0	−16 (−53·33%)
Finland	−48 (−13·68%)	−38 (−15·38%)	5 (9·26%)	−5 (−20·83%)	−10 (−38·46%)
France	−1410 (−28·96%)	−1041 (−34·28%)	−219 (−19·04%)	−101 (−31·27%)	−49 (−13·65%)
Germany	−328 (−10·53%)	−236 (−13·15%)	−46 (−6·5%)	−36 (−11·32%)	−10 (−3·4%)
Greece*	−11 (−12·22%)	−6 (−8·7%)	−2 (−14·29%)	1†	−4 (−57·14%)
Hungary	−132 (−37·29%)	−79 (−37·26%)	−27 (−39·71%)	0	−26 (−43·33%)
Italy	−525 (−16·18%)	−296 (−16·17%)	−162 (−15·25%)	−40 (−30·08%)	−27 (−12·27%)
Japan	−1413 (−66·71%)	−1112 (−69·63%)	−257 (−67·45%)	−18 (−26·47%)	−26 (−36·11%)
Netherlands	−187 (−17·64%)	−166 (−21·15%)	−7 (−4·46%)	−19 (−21·35%)	5 (17·24%)
Norway	−24 (−7·12%)	−6 (−2·99%)	3 (4·11%)	−6 (−22·22%)	−15 (−41·67%)
Portugal	−156 (−24·19%)	−67 (−19·76%)	−75 (−33·63%)	−10 (−15·62%)	−4 (−21·05%)
Slovenia	7 (8·43%)	7 (21·21%)	−2 (−9·52%)	6 (66·67%)	−4 (−20%)
Spain	−1033 (−24·02%)	−745 (−26·89%)	−176 (−18·6%)	−88 (−26·19%)	−24 (−9·68%)
Switzerland	−6 (−1·34%)	−7 (−2·69%)	−15 (−11·63%)	6 (20%)	10 (34·48%)
UK	−1298 (−31·31%)	−1076 (−35·54%)	−147 (−17·95%)	−69 (−47·92%)	−6 (−3·87%)
USA	−1370 (−4·13%)	−1110 (−5·44%)	−91 (−1·23%)	−237 (−10·18%)	68 (2·25%)
Overall	−11 253 (−15·92%)	−8560 (−19·14%)	−1714 (−10·57%)	−692 (−15·51%)	−287 (−5·44%)

Aubert et al. Lancet; 2021.

Solid organ transplantation activity and COVID-19 cases over time in Italy and Spain



ArLD listing (+7.26%; p<0.001), LT performed (+10.67%; p<0.001), AAH (+50%; p<0.001) during the pandemic



Vertical dotted lines represent the onset of COVID-19, defined as the 100th recorded case for each country. Green lines (dotted for 2019 and solid for 2020) and blue lines represent the number of organ transplants (kidney, liver, lung, and heart) and cumulative COVID-19 cases, respectively.

Aubert et al. Lancet; 2021. Cholankeril et al. Hepatology; 2021.

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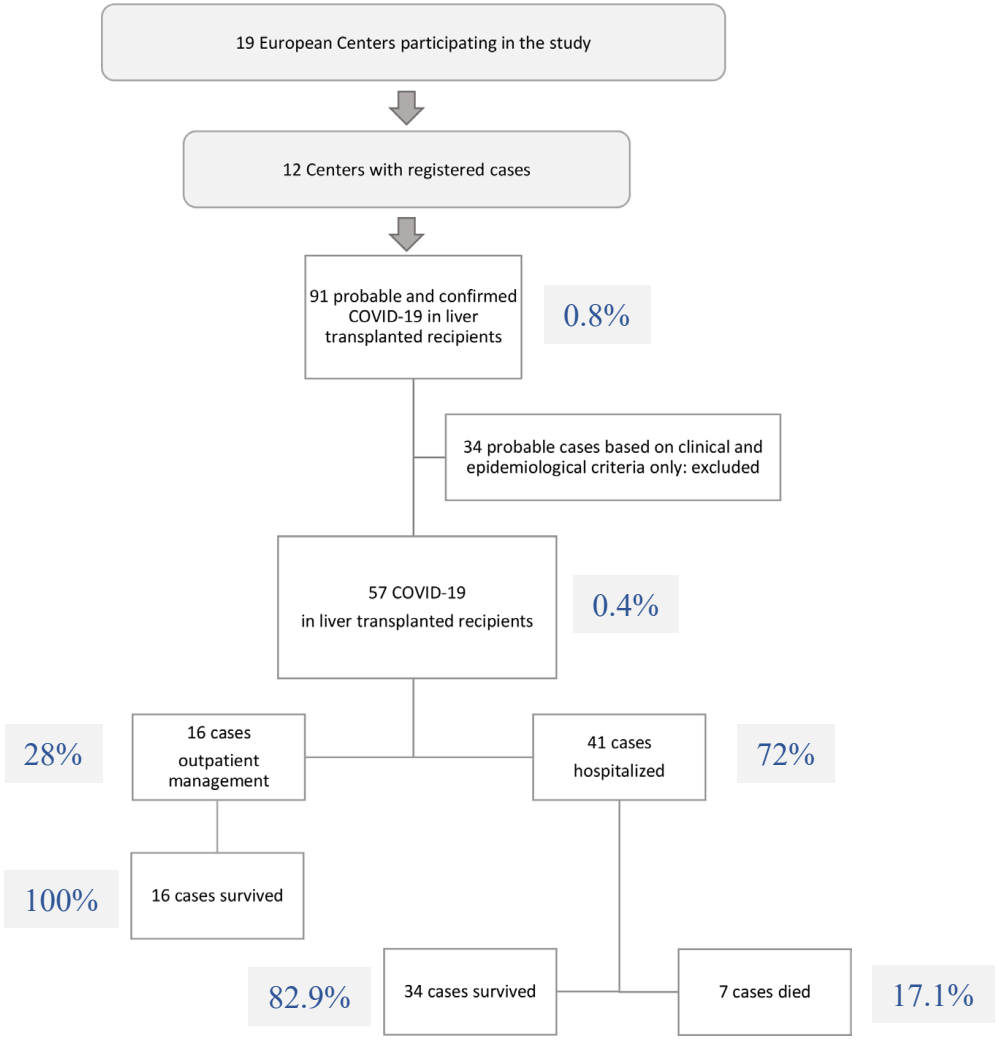
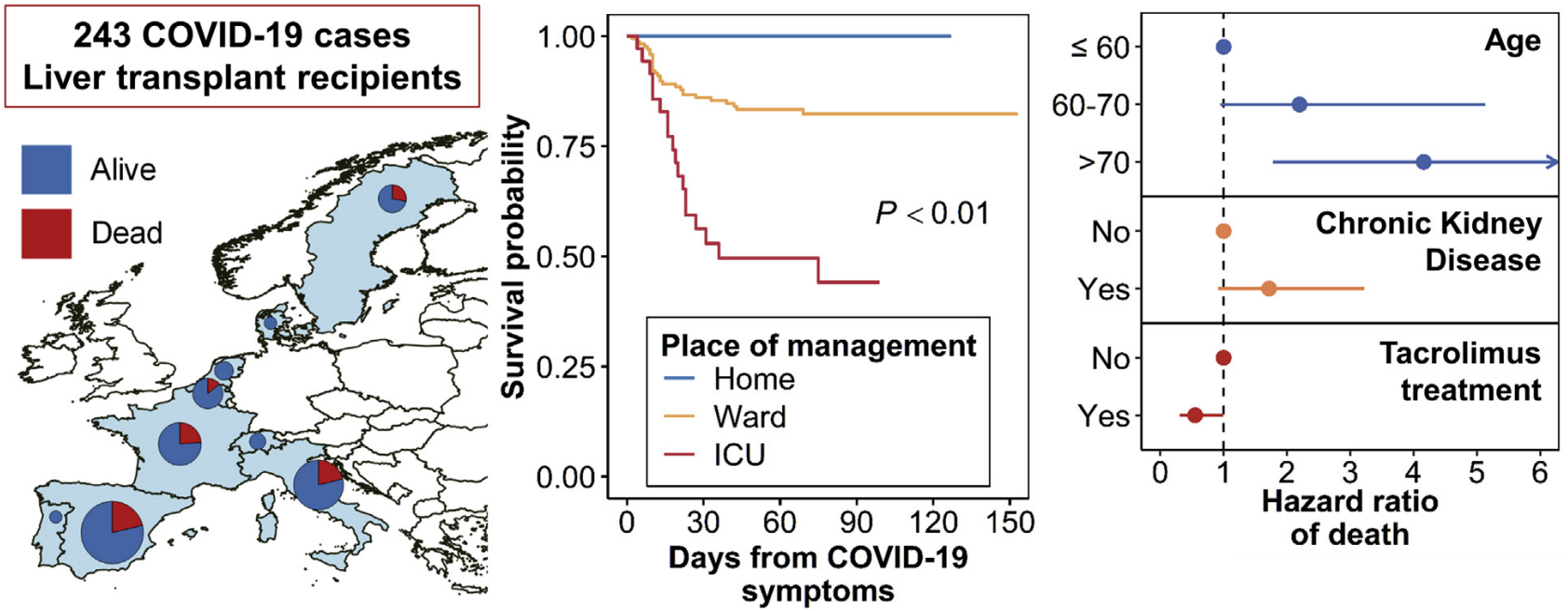
COVID-19 in an international European liver transplant recipient cohort



Becchetti, Zambelli, Toniutto et al. Gut; 2020.

Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with COVID-19



Overall mortality rate: 20%

Observation period: 1 March-27 June 2020

Belli et al. Gastroenterology; 2021.

Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients

Colmenero et al. J Hepatol; 2020.

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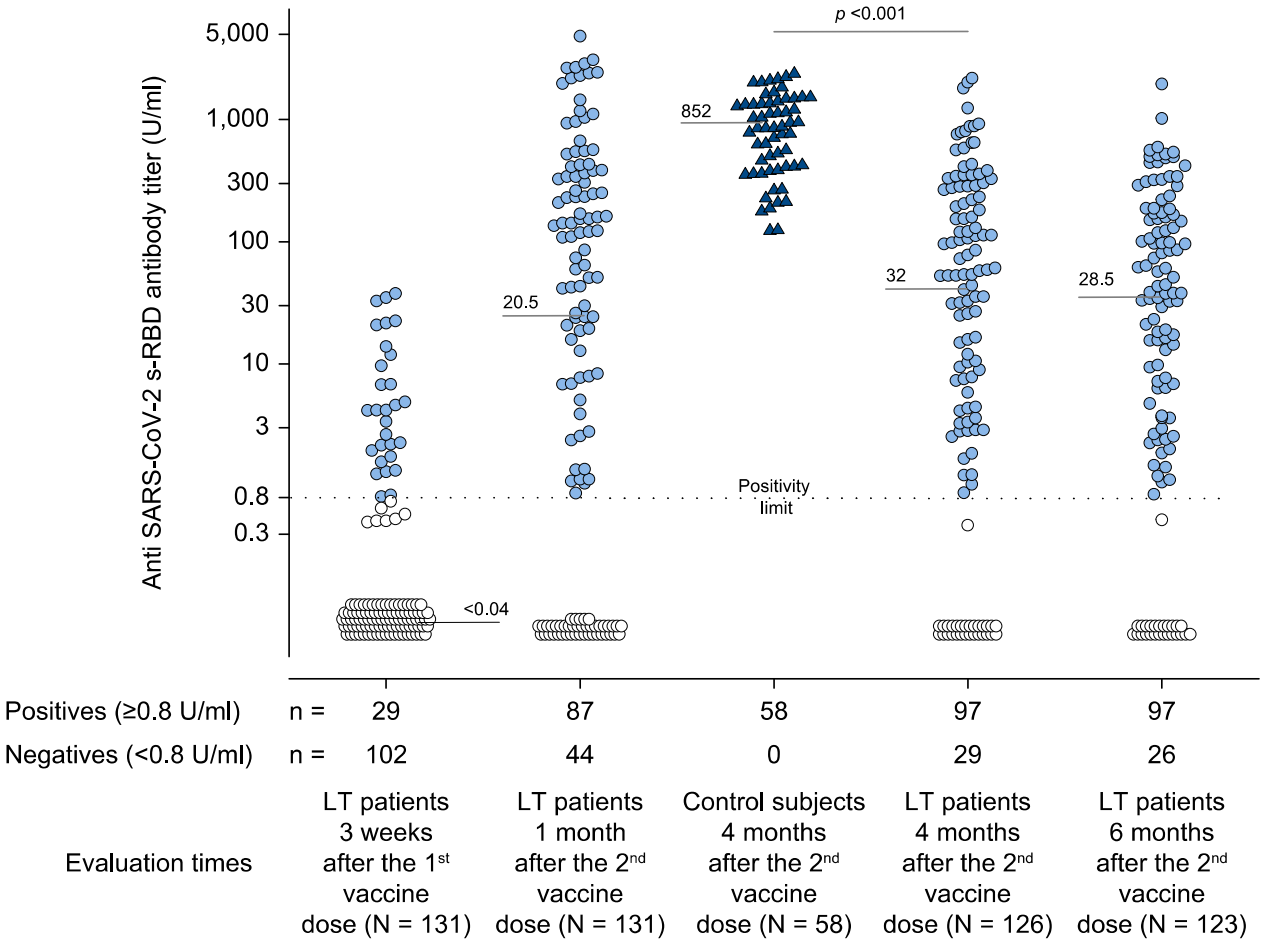
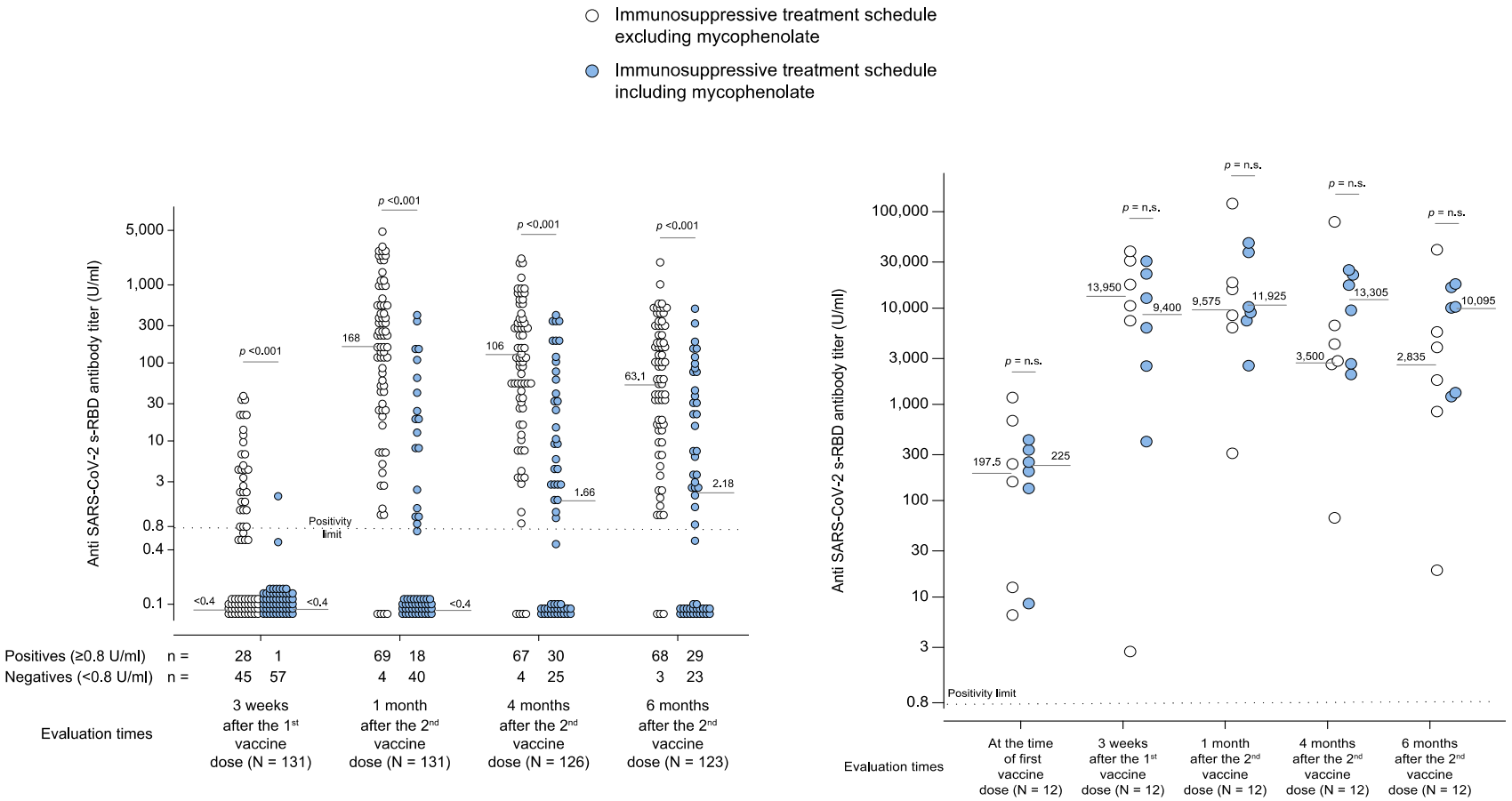
Anti-SARS-CoV-2 s-RBD antibody titers evaluated in COVID-19-naïve patients and controls after BNT16 b2 vaccination



Toniutto et al. J Hepatol; 2022.

Anti-SARS-CoV-2 s-RBD antibody titers evaluated in COVID-19 naïve and recovered patients who did or did not receive MMF following BNT16b2 vaccination

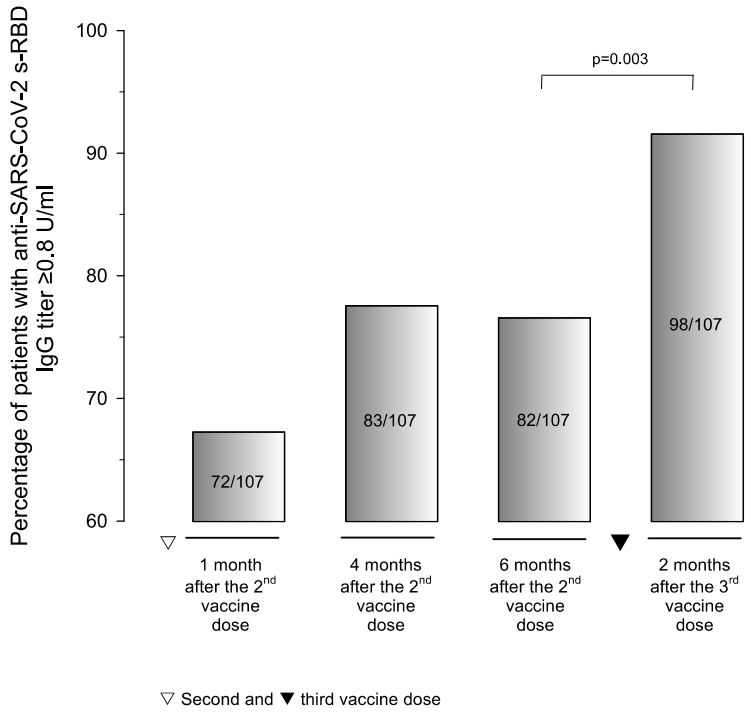


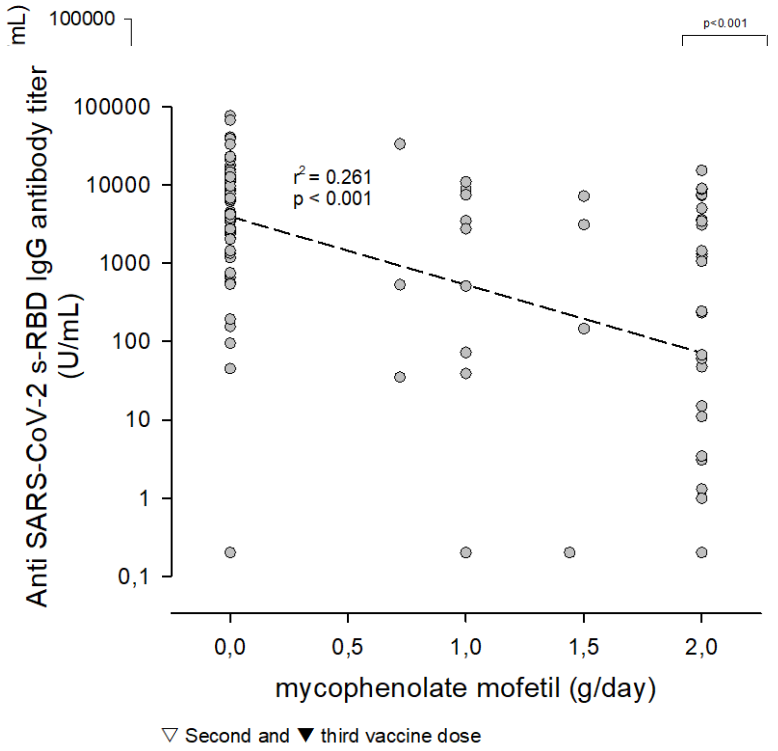
COVID-19 naive

COVID-19 recovered

Toniutto et al. J Hepatol; 2022.

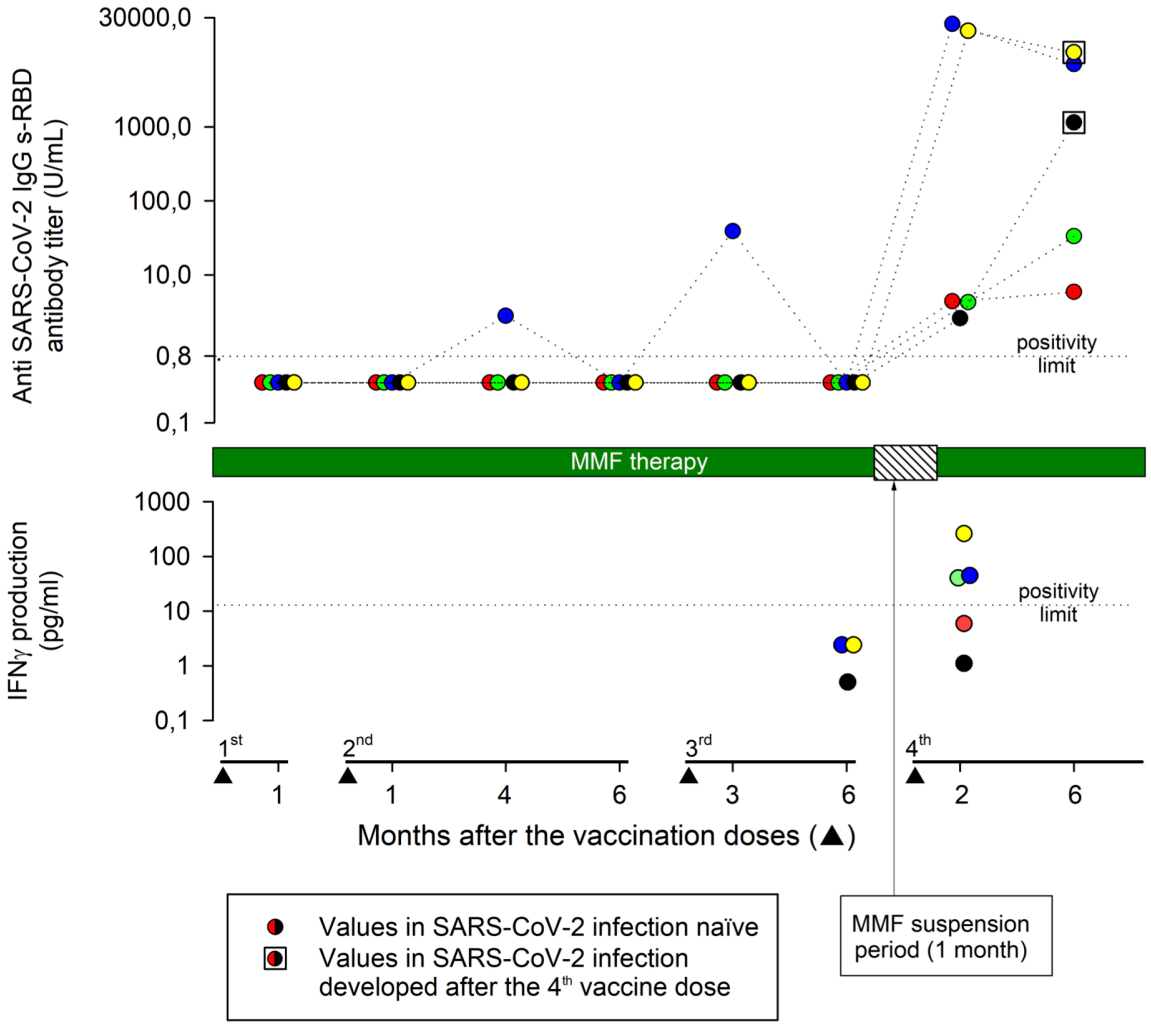
Anti-SARS-CoV-2 s-RBD antibody titers following the third dose of BNT16b2 vaccine in liver transplant recipients





Toniutto et al. Liver Int; 2023.

Impact of temporary MMF interruption in humoral and cellular immune response to the fourth dose of BNT16b2 vaccine in previously non-responder liver transplant recipients



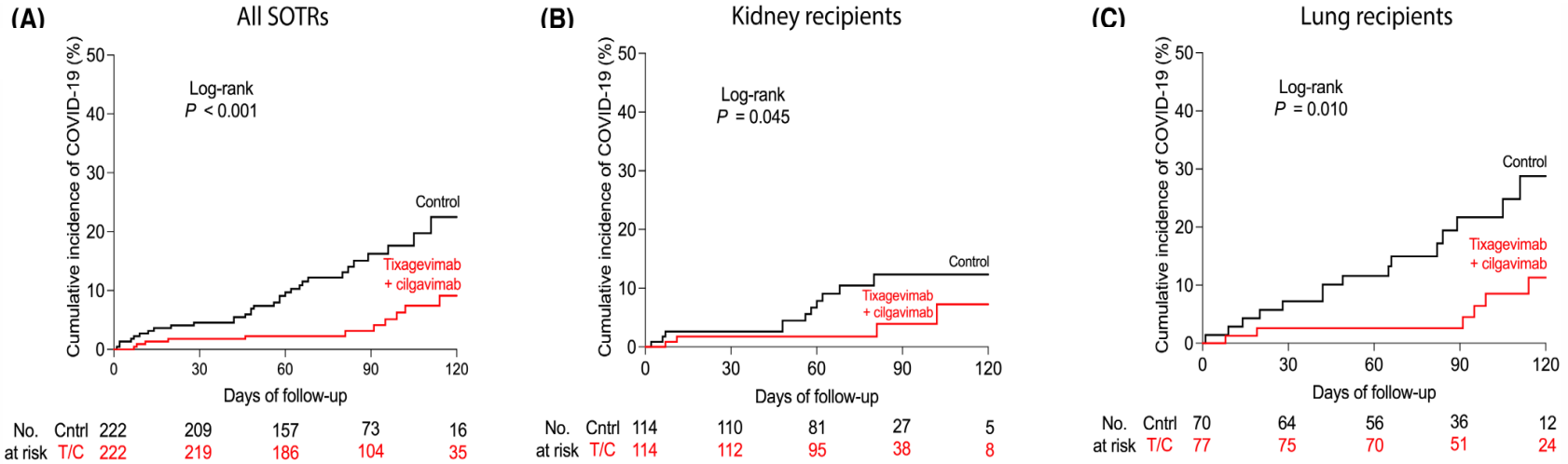
Toniutto et al. submitted; 2023.

Drugs fully authorized or authorized for emergency use in COVID-19

Drugs	Clinical indication and approval		Special consideration for LT
Antiviral			
Remdesivir (nucleotide analogue)	EMA	Hospitalised adults and adolescents* with pneumonia requiring supplemental oxygen (between 5 days and maximum 10 days) and in adults who do not require supplemental oxygen, treatment should be initiated as soon as possible after COVID-19 is diagnosed and within 7 days after symptoms appear (3 days). Approved the treatment also in paediatric population	► Not recommended if eGFR <30 mL/min due to concern for accumulation. ► Discontinue if ALT levels increase to >10 times the upper limit of normal, or if ALT elevation with signs/symptoms of liver injury. ► No interaction with IS expected
	FDA	Adults and adolescents* and who are hospitalised, or are not hospitalised and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalisation or death and authorised for emergency use for the treatment of COVID-19 in paediatric patients weighing 3.5 kg to less than 40 kg or paediatric patients less than 12 years of age and weighing at least 3.5 kg with positive results of direct SARS-CoV-2 viral testing and who (1) are hospitalised or (2) are not hospitalised and have mild-to-moderate COVID-19, and are at a high risk for progression to severe COVID-19, including hospitalisation or death	
Nirmatrelvir/ritonavir (protease inhibitors)	EMA	Treatment of mild-to-moderate COVID-19 in adults and adolescents* with positive results of direct SARS-CoV-2 viral testing, and who are at a high risk for progression to severe COVID-19, including hospitalisation or death	► Strong interaction with CNIs and mTOR inhibitor. Therefore, recommendation against co-administration
	FDA	Treatment of mild-to-moderate COVID-19 in adults and adolescents* with positive results of direct SARS-CoV-2 viral testing, and who are at a high risk for progression to severe COVID-19, including hospitalisation or death (authorised for emergency use)	
Molnupiravir (oral prodrug of beta-D-N4-hydroxycytidin)	EMA	Application for marketing authorisation	► No interactions with IS expected
	FDA	Adults with mild-to-moderate COVID-19 tested positive to direct SARS-CoV-2 viral testing who are at a high risk for progressing to severe COVID-19, including hospitalisation or death, and for whom alternative COVID-19 treatment options approved or authorised by FDA are not accessible or clinically appropriate (authorised for emergency use)	

Dofour et al. Gut; 2022.

Efficacy of tixagevimab/cilgavimab (Evusheld®) for pre-exposure prophylaxis in solid organ transplant recipients during the Omicron wave



Total number of patients: 222
Liver transplants: 17
Liver/kidney transplants: 4

Al Jurdi et al. Am J Transpl; 2022.

COVID-19 positive donor for solid organ transplantation

Summary of Italian recommendations for selection of deceased donors with previous SARS-CoV-2 infection and target recipients

Summary of Italian recommendations for selection of deceased donors with active SARS-CoV-2 infection and target recipients.

Peghin and Grossi. J Hepatol; 2022.

Liver transplantation from active COVID-19 donors

- 10 LTs with active COVID-19 donors within an Italian multicenter series
- IgG against SARS-CoV-2 at LT were positive in 80% of recipients, and 71% showed neutralizing antibodies
- SARS-CoV-2 RNA on donors' liver biopsy at transplantation was negative in 100% of cases
- 2 recipients had a positive molecular test at LT and one of them remained positive up to 21 days post-LT
- None of the other eight recipients was found to be SARS-CoV-2 positive during follow-up

Romagnoli et al. Am J Transpl; 2021.

Key point summary

- The liver transplant programs have resumed their full activity
- Mass vaccination in liver transplanted patients reduced the likelihood of SARS-CoV-2 infection and the severity of COVID-19 disease
- However, the intensity and duration of humoral and cellular responses to SARS-CoV-2 vaccination in liver transplant recipients remain lower than in the general population
- The use of COVID-19 positive donors for liver transplantation in recipients with a previous healed infection seems to have an excellent clinical outcome

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Open issues

- Future vaccination schedules
  - monitoring antibody titre and cell-mediated immunity
  - past COVID-19 Vs naïve
  - bivalent vaccines
  - role of MMF and immunosuppression
- Management of COVID-19 positive liver transplanted patients
  - in the hepatology department
  - in the infectious disease department
  - isolation mode
- Type and method of use of anti COVID-19 drugs in liver transplanted patients
- ……..