Quality and reproducibility during the COVID-19 pandemic

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In a specific context

As a result of the COVID-19 pandemic, a situation that is well known to the scientific community has recently returned to the forefront. Indeed, for many reasons (source of funding, academic promotion, competition between research teams, financial interest from the private sector, search for personal recognition), authors are tending to publish their results more and more quickly, sometimes at the price of quality and reproducibility. Scientific journals are participating in this frenetic race by offering fast track peer review trajectories that guarantee rapid evaluation by reviewers but limit the ability to evaluate the submitted work in detail. Consequently, we observe a steady increase in the number of articles that have been retracted over time, with a clear acceleration since the 2000s.[1] Publication misconduct in various forms (*e.g.* compromised peer review, plagiarism, data manipulation, *etc.*) has been reported as the most frequent reason for retraction of published articles, accounting for 28–76% of cases.[2] Some authors refer to the strategy "publish first, retract later". The problem is that often the retraction process is slow (up to 46 months according to some reports) and problematic articles remain accessible and continue to do damage in the scientific community.

We are facing a torrent of publications about COVID-19 in prestigious journals such as the *New England Journal of Medicine*, *The Lancet*, *JAMA*, *etc.* Currently, the health emergency is being used as an argument to speed up the publication of data. As of June 10, 2020, 21,172 items (original articles, journals, editorials and letters) concerning COVID-19 are referenced in PubMed for the year 2020. Many leading journals have made a call for manuscripts related to COVID-19, in some cases lowering their requirements for such data. In addition, the visibility of these publications is greatly increased through social media for the scientific community but also for the general public. One of the positive points is that contradictory debates are emerging. Nevertheless, a thorough reading of the articles and profound assessment of the methodology are sometimes missing. We are already facing expressions of concern and retractions on some very recent publications.[3] Retraction watch reports 15 retracted and 2 temporarily retracted articles concerning COVID-19 (https://retractionwatch.com/retracted-coronavirus-covid-19-papers/). This specific situation is only the exacerbation of the constant and very real challenge of scientific misconduct.

The scientific community must be aware of this threat and must continue to de-passionate debates by objectively analyzing data, with sufficient time for detailed peer review, to preserve the integrity and credibility of scientific research. The time for scientific investigation and the replicability of results is not the time of social media and fast tracks. Nevertheless, the publishers and editorial teams have a duty of transparency and wide dissemination of knowledge. They cannot neglect recent dissemination tools, bearing in mind the need to continue to follow high quality scientific standards.

This issue of JHEP Reports

It is my privilege to summarize the fourth issue of JHEP Reports in 2020. The current issue is composed of 6 original articles, 1 case-report, 1 letter and 4 outstanding up-to-date reviews by key opinion leaders on different subjects in Hepatology.

Viral hepatitis

Currently, it is well established that achieving sustained virological response (SVR) by antiviral treatments in chronic HCV infection is associated with an improvement of long-term outcomes (decreases in incidence of hepatocellular carcinoma, decompensation, listing for liver transplantation and liver-related death).[4] These data come mainly from Western countries. Few data are available from Eastern countries, particularly China.

In the current issue of *JHEP Reports*, Rao and colleagues reported the results from their prospective study of 2 parallel cohorts of patients with chronic HCV infection: from Ann Arbor in the US (n = 795) and from Beijing in China (n = 854).[5] The patients were recruited from September 2011 to July 2015 and were followed up until the occurrence of hepatocellular carcinoma, liver transplantation, death or the end of study in December 2017. The main difference between the 2 cohorts is the initial severity of liver diseases where 45% of US patients had cirrhosis compared to 16% in the Chinese cohort. About 60% of patients in the 2 cohorts received HCV treatment (interferon-free regimen in 87% of the US cohort and 42% of the Chinese cohort). Despite differences in regimen, SVR rates were similar in the 2 cohorts (87–88%). Overall, American patients more frequently experienced liver-related outcomes than Chinese patients. After a stratification for cirrhosis status, this difference was only observed for the subgroup of patients without

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cirrhosis. This observation can be explained by more advanced chronic HCV infection. Apart from a difference in severity at baseline, these data suggested that the rates of progression were similar between the cohorts. The severity of liver disease at enrollment was the best predictor of liver-related outcomes, with a 5-fold increase of risk for patients with cirrhosis compared to those without. In this study, SVR was only associated with a significant decrease in the occurrence of liver-related outcomes in patients with decompensated cirrhosis due to the fact that the follow-up was too short for the other subgroups. The safety of interferon-free regimens has led to the treatment of patients with decompensated cirrhosis. Several studies demonstrated that patients with decompensated cirrhosis achieved SVR in more than 80% of cases, with an improvement in their model for end-stage liver disease (MELD) score.[6] This major clinical progress has led to a decline of HCV as an indication for liver transplantation.[7]

NAFLD or metabolic-associated fatty liver disease (MAFLD)

It is well established that inflammatory processes and immune cells are major contributors to the liver damage observed in non-alcoholic fatty liver disease (NAFLD). The characterization of inflammatory infiltrate in the liver in humans and animal models has improved our knowledge on the pathophysiological mechanisms of NAFLD.

In this issue, Diniz *et al.* observed significant alterations in the hepatic immune system before inflammatory cell recruitment in early phases of NAFLD.[8] Liver biopsies of patients with early NAFLD (NAS 2 or 3) and livers of mice submitted to a short course of high-fat (HF) diet displayed profound modifications in immune gene expression. In particular, they observed a depletion of Kupffer cells (KCs) and a reduction in their ability to phagocytose and kill bacteria in HF mice. This early NAFLD was associated with an upregulation of Toll-like receptor (TLR)4 in mice and humans. *Tlr4*$^{-/-}$ mice submitted to the same HF diet gained more weight and had a drastically different immune gene expression. KCs from *Tlr4*$^{-/-}$ mice displayed a proinflammatory profile. Exploring the early phases of NAFLD can lead to different conclusions with regards to immune responses. Investigators must carefully address the different stages of the disease to find more suitable therapeutic targets.

Cirrhosis

Coagulation in cirrhosis is a complex issue, where the classical tests (international normalized ratio [INR], activated partial thromboplastin time [aPTT]) suggest a bleeding risk and the clinical complications (portal and peripheral vein thrombosis) suggest a prothrombotic state. The progression of cirrhosis is associated with decreases in the main coagulation and anticoagulation factors leading to a new equilibrium. In the present issue, Zermatten *et al.* performed a prospective study assessing thrombin generation with or without thrombomodulin in 260 patients with cirrhosis of differing severity.[9] They observed a decrease of thrombomodulin-mediated inhibition in cirrhotic patients compared to healthy individuals. This decrease was correlated with the severity of cirrhosis. This study confirms that INR and aPTT are inadequate markers of bleeding risk and supports a paradigm shift, with cirrhosis considered predominantly a prothrombotic state. In addition, there is some evidence that anticoagulant treatment in cirrhotic patients may prevent episodes of decompensation.[10]

Liver transplantation

One of major challenges in liver transplantation is the global organ shortage, which increases waiting list mortality.

To increase the availability of grafts, some teams use marginal grafts to reduce the mortality of their patients on the waiting list at the cost of a possible increase in post-transplant risk. In this issue, Winter *et al.* reported on the French experience of using a center-allocation (CA) system compared to the standard patient-allocation (PA) system.[11] Indeed, in France, liver grafts are allocated to patients based on the MELD score with a strategy of the "sickest first". When a liver graft is refused consecutively at least 5 times, this graft is supplied to a transplant center which can choose the recipient on the waiting list (center-allocation). The authors report an increase of 13% of graft loss/death risk in recipients of CA grafts compared to those with PA grafts. Using sophisticated statistical analysis to reduce bias, they observed that when a transplant team performed significant transplantations with CA grafts (at least 7% of their total activity) the results of CA grafts were not statistically different from those with PA grafts. This publication suggests that we can enlarge our selection criteria based on a process of learning and accumulating experience.

Another strategy is to improve the quality of the grafts and/or to limit the liver damage during preservation. Currently, flushing and static cold storage (SCS) within adequate solution is the gold-standard method but there is a lot of interest in hypothermic oxygenated machine perfusion (HOPE). The results achieved with this 'new' technology are encouraging.[12] The use of this device is limited for several reasons: cost, required medical staff, etc. A simpler solution might be to add an oxygen carrier to SCS. In this issue, Alix *et al.* compared the addition of an oxygen carrier (M101) to SCS with SCS alone and the HOPE device in a pig model of liver transplantation.[13] They observed that SCS + M101 and HOPE were better than SCS alone in different preservation parameters (oxidative stress, inflammatory mediators). After 1 hour of preservation, HOPE seemed to be better than SCS + M101. When the liver transplant was performed in pigs, the peak of transaminases was similar in SCS + M101 and HOPE and better than SCS alone. The hepatocyte necrosis and inflammatory process were lower in SCS + M101 and HOPE than in SCS alone. In the future, this strategy could represent an alternative to the use of HOPE.

Immune-related liver diseases

Autoimmune hepatitis (AIH) is classically treated with corticosteroids and azathioprine, with remission rates of around 60%. The absence of remission is a potent predictor of progression to cirrhosis and complications. Some alternative therapies have been proposed in refractory AIH but only reported as cases or small cohorts. In the present issue, Arvaniti *et al.* reported 2 cases of advanced refractory AIH treated adequately by belimumab, a human monoclonal antibody against B cell-activating factor (BAFF).[14] BAFF is produced by T lymphocytes and is implicated in the differentiation of B lymphocytes. Belimumab has been approved for the treatment of systemic lupus erythematosus. This option might be a new alternative treatment for difficult-to-treat AIH.

IgG4-related disease (IgG4-RD) is a systemic immune disorder that affects mainly the pancreas, the bile duct and the salivary glands. The diagnosis of this particular entity is challenging. The clinical presentations are pleiomorphic and the main difficulty is differentiating it from pancreatobiliary malignancies and

primary sclerosing cholangitis (PSC). IgG4 serum levels have low sensitivity and specificity. A recent study suggests that the blood IgG4/IgG mRNA ratio accurately discriminates IgG4-RD from the others (sensitivity 94% and specificity 99%) and represents a promising tool in differential diagnosis.[15] in this issue, two independent studies do not confirm these results. The first article from de Vries, Tielbeke *et al.* observed that, in a prospective observational single center study of 213 consecutive patients with a suspicion of pancreatobiliary malignancy, the blood IgG4/IgG mRNA ratio was positive (defined as ≥5%) in all patients with IgG4-RD (n = 3) and in 41% of patients with other benign or malignant disease.[16] In this study, the specificity was only 58.6%. The second study from Schulte *et al.* tested the accuracy of the blood IgG4/IgG mRNA ratio for the diagnosis of IgG4-RD in a retrospective cohort of 98 patients with different diagnosis (IgG4-RD, pancreatobiliary malignancy, chronic pancreatitis, PSC).[17] They used a cut-off range from 3.5 to 6% for positivity. The false positive results were found in 48 to 72% in cholangiocarcinoma and in 43 to 48% in pancreatic carcinoma. These 2 studies suggest that the accuracy of this IgG4/IgG mRNA ratio is insufficient for implementation in clinical practice. It remains essential to publish negative results or data not confirming previous results to ensure progression of investigations.

We hope you enjoy the issue and continue to submit your interesting investigations to *JHEP Reports*.

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TG wrote the manuscript.

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