Reviewer #1:

1. The topic of this review is interesting and the manuscript covers a wealth of information on coexisting AILDs in different SRDs and the therapeutic approach in managing these overlap diseases.
2. The structure of this review is designed properly and the manuscript is organized and presently well. The readers may feel better if the length of introduction can be shortened.

Response:

Since the major cause of abnormal liver function test in patients with SRDs is associated with drugs, one reviewer required us to include a new table regarding the safety of commonly used medications in the liver. Therefore, there were 3 tables in the Introduction section of the revised manuscript. Furthermore, we have added comments on immune checkpoint inhibitors-related hepatotoxicity in the introduction of revised manuscript as requested by another reviewer. Nevertheless, following your valuable suggestion, we have abbreviated the length of Introduction in the revised manuscript as possible.

3. Distinguishing liver involvement in SRD from AILD and identifying the overlap of AILD and SRD is important at an early stage since such a coexistence

may influence the disease course and prognosis. The data about the prevalence and characteristics about SLE-AIH overlap diseases have been listed in detail. It would be better if there is more detailed description on how to distinguish them and their characteristics in other overlap diseases.

Response:

Indeed, in AILDs, it is important to identify the overlapping SRDs at an early stage since such a coexistence may influence the disease course and prognosis. Commonly co-occurring SRDs in AILDs are Sjögren syndrome (SS), rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) in autoimmune hepatitis (AIH), and SS, RA or systemic sclerosis (SSc) in primary biliary cholangitis (PBC). Furthermore, owing to different disease complications and therapies, it is imperative to differentiate between SLE liver involvement (lupus hepatitis) with mild presentation and SLE-AIH overlap with severe disease.

In this review article, we have thoroughly described clinical prevalence and disease characteristics of the SLE-AIH overlap disease, and described in detail the differentiation between SLE-AIH overlap and lupus hepatitis. We also discussed other commonly observed overlap disorders including SS-AIH, SS-PBC, RA-AIH, RA-PBC and SSc-PBC. Nevertheless, since this is a mini-review article, we only made limited discussion on other infrequently encountered overlap diseases.

Reviewer #2:

I would like to congratulate the authors for their sincere efforts to simplify the one of the most complicated and ignored topic. Treatment part is not discussed adequately in the review. I have some suggestions, the inclusion of which will results in the completeness of the topic.

1. First, needs to discuss about Psoriatic arthritis and its effects on liver.

Response:

Following your suggestion, we have added the discussion on psoriatic arthritis and its related hepatic abnormalities with a paragraph in pages 14 to 15 and as follows.

Psoriatic arthritis (PsA) is a less common SRD with psoriasis (PsO) and inflammatory arthritis, associating with extra-articular manifestations which have an impact on their therapeutic regimens[141]. Similar to RA, liver enzyme abnormalities in PsA and PsO can be caused by comorbid NAFLD and used medications including NSAIDs and conventional or biologic/targeted SDMARDs. Despite an increased association of AIH in PsA and PsO[142], these patients might be under anti-TNF therapy, and both diseases are commonly observed complications in ATIAIH[138].

2. Secondly, in systemic autoimmune diseases, use of herbs or ayurvedic medication are common, which often results in DILI, apart from NSAIDs, or DMARDs. Moreover, a mentioning should be there that a low dose

methotrexate is safe, and we should not just make methotrexate culprit, without ruling out the other causes or coexistent metabolic effects of uncontrolled systemic autoimmune diseases, can results in liver dysfunction, and therefore adequate control of systemic autoimmune diseases is required.

3. Thirdly, a table should be dedicated to the treatment aspect, regarding the safety of commonly used DMARDs and biological agents in liver diseases, including psoriatic arthritis. My suggestions to include theses to change the clinical practice and remove the fear of using DMARDs in liver dysfunctions and precautions to be followed.

Response:

Following the valuable comments, we have revised the discussion in the Introduction section in the page 1 as follows. High occurrences of DILI in SRDs are due to ----- the use of herbal or ayurvedic compounds. Despite the relative safety with a low-dose prescription, methotrexate, a SDMARD frequently used in SRD-related arthritis -----.

Furthermore, we have created a new Table 1 in the revised manuscript to describe the therapeutic aspect related to the hepatic safety of commonly used medications in SRDs including those used in psoriatic arthritis patients, e.g., apremilast and ustekinumab. In particular, this table had included the Likelihood score category in

DILI with A- definite, B- highly likely, C- probable, D- possible, E- unlikely and E*- suspected, to remove the fear and emphasize that most used medications are not in the A category and some drugs are in the E/E* category.

Reviewer #3:

This is an excellent review and I think it is important for practicing gastroenterologists and hepatologists.

1. The traditional levels of elevated ALT are no longer accepted with an ULN of 19 for women. How would this change the liver involvement in autoimmune disease?

Response:

Previous studies have suggested that the upper limit of normal (ULN) of serum ALT levels should be revised and there is a recommendation of 19 U/L for women, lower than earlier recognized ULN levels. In the Introduction section, we have pointed out that although SRDs can have liver involvement, most patients only have abnormal liver enzymes without significant changes in histopathology[2,3]. Since common AILDs like AIH and PBC are female predominance, when raising a suspicion on coexistent AILDs in patients with SRDs, rheumatologists and hepatologists should pay attention to the female ULN for serum ALT levels. Nevertheless, the ULN of ALT could be re-evaluated by different countries with individual ethnic groups (Ref. PLoS ONE

2012;7:e437360)

2. Checkpoint inhibitors can produce immune liver damage and other immune diseases. Perhaps some comment on this area which will increase in the near term future. I think a comment about the high level of serum ferritin in Stills disease is necessary in order to avoid unnecessary investigation of hemochromatosis.

Response:

Following the valuable comments, we have discussed on the liver dysfunction caused by checkpoint inhibitors and the hyperferritinemia in AOSD on page 5 and page 17, respectively, in the revised manuscript as follows.

Although immune checkpoint inhibitors have altered the therapeutic paradigm in oncological patients, there is undesirable off-target autoimmune reaction causing adverse effects like musculoskeletal manifestations and immune hepatitis, a pan-lobular active hepatitis resembling AIH[9].

In medical practice, hyperferritinemia is a non-specific finding related to iron overload in only 10% of cases such as hereditary hemochromatosis, while underlying causes attributing to a reactive increase in the rest 90% patients such as AOSD[168].