**Response to reviewers’ comments**

I am very much thankful to the editor sand reviewers for their deep and thorough review Thank you for your efforts.

The required changes were done and highlighted in revised manuscript.

**the manuscript has been rewritten according to the plagiarism report and reviewers suggestions regards grammar corrections**

**Response to reviewer 1**

Comment 1: In the subject’s section: IWCLL (stands for?)

Response 1: Thank you for pointing this out. In the revised manuscript we added list of abbreviations includes, IWCLL: International Workshop on Chronic Lymphocytic Leukemia

Comment 2: Please unify the writing style of the references. For example, some of them had DOI, and others did not.

Response 2: Thank you for your comment. In the revised manuscript we have re writing the references according to style of the references

Comment 3: - Table 1: the control group: 100 25 (100%) =, in all the number, is 25, not 100

Response 3: Thanks again. In the revised manuscript we reanalysis our date by SPSS and correct the table according to reviewers’ suggestions.

Comment 4: Table 2: total bilirubin difference was significant 0.7943 (0.022). You should mention the statistical test applied below each table.

Response 4: Thanks again. In the revised manuscript we reanalysis our date by SPSS and correct the table according to reviewers’ suggestions.

Comment 5: Table 3: HCV prevalence 0.003 (0.6392) non-significant, ZAP 70% 0.006 (0.3912) non-significant, CD 38% 0.012 ( <0.0001) and this could affect the results, please revise it

Response 5: Thank you for your silent observations, in the revised manuscript we reanalysis our date by SPSS and correct the table according to reviewers’ suggestions.

**Response to reviewer 2:**

**Check the uploaded file.**

Response 1: The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment1 :Please revise the title according to the inclusion criteria and the percent of hcv patients in the result

Response 1: the title of the research ‘’ Assessment of miR-150-5 p as diagnostic and prognostic markers of B- chronic Lymphocytic Leukemia in chronic hepatitis C ‘’.and the current study aimed to investigate the role of miR-150-5 p expression as a diagnostic and prognostic marker of B- CLL among Egyptian patients with chronic hepatitis C and its impact on risk stratification and response to therapy. According to results we detected non-significant and significant results as we mentioned in the revised manuscript and so we don’t need to re title the research .

Comment2: Please add the name of extraction kit and cat n

Also for RT kits, name of normalization miRNA 'housekeeping' and RTPCR reaction content and condition

Response 2: Sorry, according to the recent promotion requests we need low similarity in plagiarism when we add the details of the laboratory techniques we will reach un accepted level of similarity.

Comment 3: What is the meaning of B symptoms in table 1

specific B symptoms such as weight loss, night sweats, and fever

Response 3: Thank you for your silent observations, yes, we meant that by B symptom as we mentioned in flowchart of the study.

Comment 4: According to figure 1 and title the inclusion criteria include HCV patients, explain or revise why 76% of patients not infected.

Response 4: Thank you for your silent observations, the prevalence in the current study not in Egypt as the current study was case control study not cross sectional studies so we could not correctly calculate the prevalence in whole country .

Comment 5: Revise according to inclusion criteria in figure 1 and title

Response 5: According to results we detected non-significant and significant results as we mentioned in the revised manuscript and so we don’t need to re title the research .as the sample size was small and we added limitation and recommendation of the study regarding to these limitation.

Comment 6: in the un treatment subgroup compared to successfully treated subgroups.

Response 6: The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 7: Add limitation and recommendation of the study.

Response 7: The required changes were done and highlighted in revised manuscript in response to reviewer comments.

**Response to reviewer** 3:

Comment1 : 1- please clarify for me your research topic and inclusion criteria how it is for HCV-positive patients, and in clinical criteria, you included only six patients positive for HCV, although you are in an endemic area for HCV

Response 1: Thank you for pointing this out. We agree with this comment. We had limitation in the current study regarding small size study and this study design was case control study not cross sectional study and we added limitations of the study as recommended by reviewers .As I have mentioned before, the sample size and design was performed according to IRB committee recommendations.

Comment 2- although you gave your patients ibrutinib, you did not mention any data about 17p deletion. Is it done for the patients, and how many positives?

Response 2: Thank you for your silent observations. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 3: no response mentions although you told successful treatment or survival outcomes to support your recommendation as prognostic and predictive.

Response 3: Thank you for your silent observations. The treated group were good response during study duration. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 4: discussion needs to be written again, as the last part is the repetition of the result.

Response 4: Thank you for your silent observations. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 5:English editing is needed.

Response 5: Thank you for your silent observations. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

**Response to reviewer 2:**

Comment 1 THE TITLE: needs to be edited “**Assessment of miR-150-5 p as diagnostic and prognostic markers of B- chronic Lymphocytic Leukemia in chronic hepatitis C”**

Response 1: Thank you for your silent observations. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 2: In introduction: it’s better to start speaking about HCV from the beginning of a separate paragraph.

This sentence needs to be edited: Hepatitis C virus (HCV) is a hepatotropic and lymphotropic virus and its infection affects the B lymphocytes compartments.

Response 2: Thank you for your silent observations. The required changes were done and highlighted in revised manuscript in response to reviewer comments.

Comment 3: INTRODUCTION: The first two sentences of the last paragraph need references

Response 3: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

Comment 4: METHOD: The sequence of miRNA STEM LOOP is missing. Also, the housekeeping gene is missed (usually U6). Moreover, a reference for the sequence is required. Regarding house keeping gene war corrected in the revised manuscript

Response 4: Sorry, according to the recent promotion requests we need low similarity in plagiarism when we add the details of the laboratory techniques, we will reach un accepted level of similarity.

Comment 5: METHOD: a brief explanation of the miRNA expression method (steps and used devices and kits) and analysis (method of measurement of fold expression) is missed.

Response 5: The relative expression level was determined using the 2-ΔΔCT method as we mentioned in the last paragraph of methods. Regards the details of methods I mentioned the response in the previous response.

Comment 5: Sample size is too small particularly in subgroup comparison.

Response 5: Thank you for pointing this out. We agree with this comment. But the sample size was calculated according to IRB committee recommendations.

Comment 6: RESULTS: the first sentence is better transferred to discussion (results section is commonly for representing data analysis not for justification)

Response 6: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

Comment 7: RESULTS: needs to be edited “concerning severity and diagnostic markers, LDH, serum β2M, ZAP-70% and CD38% were significantly higher in CLL group compared to controls”. So, I recommend English editing

Response 7: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

Comment 8: - SUBJECTS: it was mentioned that periodic monitoring every 3 months was performed. Where are the follow up data also, it is not clear when sampling was performed at the beginning of the study or at the end of follow up period (to be noted that some chemotherapeutics affect gene expression pattern)

Response 8: Thank you for pointing this out. The periodic monitoring every 3 months was performed to assess the patients if they need chemotherapy or not .Regards the sample , we have taken at the beginning of the study or at the end of follow up period, and we have mentioned the impact of chemotherapy on miRNA on table 3 as chemotherapy treatment leads to increase miRNA and this results was interesting as we could use miRNA as prognostic markers .

Comment 9: - RESULTS: miR-150-5 p expression in the control group was 0.88±0.12 (the average should be around 1. What was the method of calculation of fold expression)?

Response 9: The relative expression level was determined using the 2-ΔΔCT method as we mentioned in the last paragraph of methods.

Comment 10: DISSCUSION: This paragraph needs to be edited “Several studies reported HCV infects not only hepatocytes but also extrahepatic cells for example B lymphocytes [11], contributing to the oligoclonal proliferation of the infected B-cells, and then the presence of HCV in lymphocytes could initiate growth dysregulation and predispose the lymphocyte to development of further molecular changes, malignant B-cell lymphoproliferative disease, for example, CLL”

Response 10: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

Comment 11 :“WBC, ALC, hemoglobin, platelets, LDH, serum β2M, ZAP-70% and CD38%” all these markers were mentioned in results without explanation in methodology section how, when and where were they performed. Also, there is no mention of method of HCV infection detection.

Response 11: we have mentioned in the flowchart and section of methods that and testing was done according to operating techniques in Zagazig university hospital and Medical Biochemistry laboratories as shown in figure1

Sorry regards the details , we could not write it as it shows high similarity according to the recent promotion requests we need low similarity in plagiarism when we add the details of the laboratory techniques we will reach un accepted level of similarity.

Comment 12: RESULTS: “about 19 (76%) of CLL patients not infected with HCV and 6 (24%) of CLL patients infected with HCV”. Was it a random sample this means that the prevalence of HCV in CLL patients in Egypt is around 24% are there any evidence for that from previous publications?

Please revise the following publication “6.3% of CLL patients and 2.8% of healthy controls tested positive for previous or ongoing HBV infection while 1.8% of CLL patients and 1.4% of controls tested positive for HCV markers”

Minuk GY, Lerner B, Gibson SB, Johnston JB, Uhanova J, Andonov A, Wu J. Hepatitis B and hepatitis C viral infections in patients with chronic lymphocytic leukemia. Can J Gastroenterol Hepatol. 2014 Mar;28(3):131-4. doi: 10.1155/2014/780350. PMID: 24619633; PMCID: PMC4071875.

given that the high prevalence of HCV in Egypt (mean HCV prevalence was estimated at 11.9%), can it justify the previous result that quarter of patients had HCV

From the above, it is necessary to understand the nature of participants and inclusion criteria

Response 12: Thank you for your silent observations, the prevalence in the current study not in Egypt as the current study was case control study not cross sectional studies so we could not correctly calculate the prevalence in whole country .

Comment 13: DISCUSSION: this sentence needs editing” Similar results detected by Mraz et al postulated that ~~miR-150~~ low-level expression of miR-150 was associated with unfavorable clinical and prognostic markers of CLL

Response 13: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

Comment 14: DISCUSSION: the authors said “Interestingly, there were significantly lower levels of miR-150-5 p in the treatment subgroup compared to successfully treated subgroups. As a matter of fact, treatment of patients with CLL increase miR-150-5 p levels. I think its no treatment group

Response 14: Thank you for pointing this out. In the revised manuscript The required changes were done and highlighted in response to reviewer comments.

**Response to Editor Comments:**

I am very much thankful to the editor sand reviewers for their deep and thorough review Thank you for your efforts. The required changes were done and highlighted in revised manuscript We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

The corresponding author