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International Journal of Advanced Research

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REVIEWER'S REPORT

Manuscript No.: IJAR-58260

Title: THYROID DYSFUNCTION IN PATIENTS TREATED WITH ANTI-HCV ORAL DIRECT ACTING ANTIVIRAL THERAPY.

Recommendation:
Accept as it is .....
Accept after minor revision.....
Accept after major revision -YES
Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality		_		
Techn. Quality			_	
Clarity			_	
Significance	_			

Reviewer's ID: JPR-094

Detailed Reviewer's Report

 # Reviewer's Report

*****Manuscript Title:** *Thyroid Dysfunction in Patients Treated with Anti-HCV Oral Direct Acting Antiviral Therapy****

Overall Evaluation

This manuscript presents a multicentre prospective cohort study investigating the prevalence of thyroid dysfunction following treatment with direct-acting antiviral (DAA) therapy in patients with chronic hepatitis C infection. The topic is clinically relevant because DAAs have largely replaced interferon-based therapy, yet their endocrine safety profile remains incompletely understood. The study includes 280 patients and reports a 33.6% prevalence of thyroid dysfunction, predominantly hypothyroidism, with a significantly higher prevalence among female patients.

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 # Strengths

1. Clinically Relevant Topic

**** The study addresses an important clinical issue regarding thyroid dysfunction after DAA therapy, an area with limited regional evidence.***
**** The research question is clearly defined.***

2. Prospective Multicentre Design

**** Prospective cohort methodology reduces recall bias.***
**** Inclusion of three tertiary hospitals improves external validity within Pakistan.***

3. Adequate Sample Size

**** A total of 280 patients were included.***
**** Sample size calculation is described.***

4. Well-defined Inclusion and Exclusion Criteria

**** Patients with previous thyroid disease and other confounding conditions were excluded.***

5. Appropriate Statistical Analysis

**** Descriptive statistics are appropriate.***
**** Chi-square test is suitable for categorical comparisons.***

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**** P-values are reported.***

6. Ethical Compliance

**** Ethical approval and informed consent are documented.***

7. Good Discussion

**** Results are compared with several recent international studies.***
**** Authors discuss possible biological explanations.***

 # Weaknesses

Major Weaknesses

1. No Control Group

The study lacks a treatment-naïve or healthy control group, making it difficult to determine whether thyroid dysfunction is attributable to DAA therapy or underlying HCV infection.

2. Short Follow-up

Only a 3-month follow-up was performed.

Delayed thyroid dysfunction could have been missed.

3. No Baseline Thyroid Antibody Testing

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The study does not evaluate:

**** Anti-TPO antibody***

**** Anti-thyroglobulin antibody***

Therefore autoimmune thyroid disease cannot be differentiated.

4. Limited Statistical Analysis

Only Chi-square analysis was performed.

The manuscript would be strengthened by:

**** Multivariable logistic regression***

**** Odds ratios***

**** 95% confidence intervals***

to identify independent predictors.

5. Possible Selection Bias

Non-probability consecutive sampling may introduce selection bias.

6. Single Country Population

Results may not be generalizable outside Pakistan.

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7. Incomplete Description of Laboratory Methods

The manuscript should specify:

** Laboratory analyzer*
** Manufacturer*
** Assay method*
** Internal quality control*
** Reference intervals*

 # Minor Weaknesses

** Numerous grammatical and typographical errors.*
** Inconsistent spacing.*
** Formatting issues throughout the manuscript.*
** Several references require uniform journal style.*
** Tables need better formatting.*
** Units should be standardized.*

 # Key Points

** Prospective multicentre cohort of **280 HCV patients** receiving Sofosbuvir + Daclatasvir.*
** Thyroid dysfunction prevalence was **33.6%**.*

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**** Hypothyroidism (28.6%) was much more common than hyperthyroidism (5%).***

**** Female patients had significantly higher thyroid dysfunction.***

**** Age was not significantly associated with thyroid dysfunction.***

**** Authors recommend routine thyroid function monitoring before and after DAA therapy.***

 # Scientific Significance

Originality: Good

Although thyroid dysfunction after interferon therapy has been widely studied, fewer prospective studies have evaluated thyroid abnormalities following oral DAA therapy, particularly in South Asian populations.

Clinical Significance: High

The findings suggest clinicians should consider thyroid function monitoring in HCV patients receiving DAA therapy, especially women.

Public Health Importance: Moderate to High

Given the high prevalence of hepatitis C in Pakistan and increasing DAA use, the study has regional public health relevance.

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Research Impact: Moderate

The study provides useful observational data but lacks mechanistic evidence and multivariable analysis.

 # Reviewer Recommendation

*## **Recommendation: Major Revision****

Justification

The manuscript addresses an important clinical question and has several strengths, including a prospective multicentre design, adequate sample size, and clinically relevant findings. However, significant methodological and reporting limitations need to be addressed before publication.

The authors should:

**** Improve English language and formatting.***
**** Expand statistical analyses using multivariable methods.***
**** Provide detailed laboratory methodology.***
**** Discuss potential confounding factors more thoroughly.***
**** Clarify study limitations.***
**** Strengthen the discussion regarding causality.***
**** Ensure consistency in references and manuscript formatting.***

After satisfactory revision, the manuscript may be suitable for publication.

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 # Overall Rating

Parameter	***Rating***
Originality	***Good***
Technical Quality	***Good***
Scientific Merit	***Good***
Clinical Relevance	***Excellent***
Methodology	***Fair to Good***
Statistical Analysis	***Fair***
Presentation	***Fair***
Discussion	***Good***
References	***Good***
Overall Recommendation	*****Major Revision*****

Based on a detailed review of the manuscript, I recommend **Major Revision** rather than acceptance because there are several methodological and reporting issues that affect the scientific strength of the paper. The study addresses an important topic and has merit, but the current version requires substantial improvements before it is suitable for publication. The manuscript investigates thyroid dysfunction after direct-acting antiviral therapy in hepatitis C patients and reports a 33.6% prevalence of thyroid dysfunction.

Justification for Major Revision (Issue-wise)

No.	Issue	Why it Requires Major Revision
1	**Absence of a control group**	The study includes only patients treated with DAA therapy and lacks either a treatment-naïve HCV group or healthy controls. Therefore, it is impossible to determine whether thyroid

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No.	Issue	Why it Requires Major Revision
		dysfunction is caused by DAA therapy or by chronic HCV infection itself. This limitation directly affects the validity of the study conclusion. The authors also acknowledge this limitation.
2	**Short follow-up period (3 months)**	Thyroid abnormalities may develop several months after antiviral therapy. A three-month follow-up may underestimate delayed thyroid dysfunction and long-term outcomes. This limits the clinical significance of the findings.
3	**No thyroid autoantibody assessment**	The study measures only TSH, FT3 and FT4. Anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies were not evaluated, making it impossible to distinguish autoimmune thyroid disease from non-autoimmune dysfunction. This weakens interpretation of the mechanism.
4	**Limited statistical analysis**	The analysis is restricted mainly to descriptive statistics and Chi-square testing. There is no multivariable logistic regression to identify independent predictors while adjusting for confounders such as age, sex and viral load. This reduces the robustness of the conclusions.
5	**Potential selection bias**	Participants were selected using non-probability consecutive sampling, which may not represent the broader HCV population and limits external validity.
6	**Insufficient laboratory methodology**	The manuscript does not specify the analyzer, assay manufacturer, assay principle, quality control procedures or laboratory accreditation. These details are necessary for reproducibility and scientific transparency.
7	**Overstated conclusions**	The conclusion recommends routine thyroid screening after DAA therapy. However, because the study lacks a control group and adjustment for confounders, causality cannot be established. The recommendation should be presented more cautiously.
8	**Incomplete discussion of confounding factors**	Important variables such as nutritional iodine status, autoimmune disease, family history of thyroid disorders and other endocrine disorders were not evaluated or discussed. These factors could influence thyroid dysfunction independently of DAA therapy.
9	**Generalizability is limited**	Although multicentre, all centres are located in Pakistan and involve a single ethnic population. Therefore, findings may not be applicable to other populations. The authors appropriately acknowledge this limitation.

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No.	Issue	Why it Requires Major Revision
10	**Language and formatting problems**	Numerous grammatical errors, spacing inconsistencies, punctuation problems and formatting issues reduce readability and require professional language editing before publication. These do not invalidate the science but require substantial revision.

Why Not Reject?

The manuscript also has several strengths that justify revision instead of rejection:

It addresses a clinically important and relevant topic.

The study uses a prospective multicentre design.

The sample size (280 patients) is adequate.

Ethical approval and informed consent were obtained.

The discussion compares findings with recent international literature.

The results provide useful regional data where evidence is limited.

Overall Reviewer Recommendation

Recommendation: Major Revision

Reason: The manuscript has scientific value and the data are potentially publishable, but important methodological limitations, insufficient statistical analysis, incomplete laboratory reporting, overinterpretation of findings, and presentation issues must be addressed before the work can be considered for publication. These concerns are substantial enough to require **major revision**, but they do not warrant outright rejection because they are, to a considerable extent, addressable through revision.