



**Baishideng
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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer’s code: 02521807

Reviewer’s country: Argentina

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-08-27

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Please find below the main criticisms observed by this reviewer:

- 1 The title reflects the main subject of the manuscript
- 2 The abstract summarizes and reflects well the work described in the manuscript
- 3 The key words reflect the focus of



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the manuscript. 4 The manuscript adequately describe the background and significance of the study. However, it should be ordered.

5 Taking into consideration that the review topic is a hot one, it is recommended to explain the methodology used to search in different bibliography databases.

A methodology section is added (page 4)

How the authors have carried out the search?

A comprehensive literature search was performed and research papers regarding non-cirrhotic HCC and related literature was analyzed to prepare this review article. Special emphasis was placed on research related to the diagnosis and management of non-cirrhotic HCC in the last 5 years

which period of time havebeen involved?

Special emphasis was placed on research related to the diagnosis and management of non-cirrhotic HCC in the last 5 years

How have they prioritized the information and made data analysis in adequate detail?

A detailed data analysis was made searching the pubmed, scopus, Cochrane databases to ensure coverage of the topic in detail.

6 What are the contributions that the review has made for research progress in this field?

A section on contribution is added in the manuscript.

Contribution title is included that lists the contribution made by this review.

According to authors opinion it is only a modern one. But, for specialized readers it should be more explicated.



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7 For this reviewer the manuscript did not prioritize some topics in the text. As example, the causes that promote HCC are enlisted but not categorized which would be beneficial for readers.

The risk factors are listed in the order of priority to ensure benefit to the readers.

Similarly the available diagnostic tools should also be categorized according to their usefulness.

Similarly diagnostic tools are also enlisted in the order of priority. For example US as the initial screening tool followed by CT scan and MRI.

Some terms appear described only for specialists but not for unexpert readers (i.e. "BCP T1762/A1764 mutation..." page 5)

Since the review is directed towards both expert and non-expert readers some specialized information such as BCP T1762/A1764 mutation is used

8 The figures, and CT images should be more clear. In example, the authors should indicate with arrows tumoral mass for easier visualization.

Thank you for this comment. Images have been redesigned according to the suggestion.

It is important to define that images are property of the authors and clarify the legends.

Thank you for this comment. It is mentioned in the main text and the legends are detailed out.

9 The manuscript did not included any biostatistic analysis.

10 References. The manuscript references are unappropriately cited .

Thank you for this comment. The references are now cited according to the journal's requirement.



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INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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- No

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer's code: 02444752

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-08-31

Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This review was well written and informative, but the references should be formatted according to "instruction to authors".

We thank the reviewer for this valuable comment. References are now formatted



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according to the journal's directions.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer's code: 02861252

Reviewer's country: Turkey

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-09-01

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Very specific and important issue. Thank you for good research suggestions.

We thank the reviewer for appreciation of this important review.



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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer's code: 02942798

Reviewer's country: Slovakia

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-09-02

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear sir, thank you to select me to review manuscript: Desai A et al. Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review. Paper summarizes epidemiology, risk factors, diagnostic methods and management of hepatocellular cancer (HCC) in non-cirrhotic liver. Manuscript is well written, but some changes are



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recommended:

1) Not only MetSy and obesity, but also overweight is associated with higher risk of HCC. Overweight and obesity increase HCC prevalence in general population and especially in HBV and HCV patients (Rahman R et al. World J Gastrointest Oncol. 2013;5(9):186-94. doi: 10.4251/wjgo.v5.i9.186).

Thank you for this comment. This information and the reference is now included in the main text of the manuscript (Page 6, line 10).

2) HBV viral load is an independent risk factor for HCC in patients with chronic hepatitis B. Please comment these data in special paragraph.

Thank you for this comment. This has been addressed now included in the maintext (page 6, last 3 lines).

3) F3 fibrosis in NAFDL, HBV and HCV patients is associated with high risk of developing HCC. Please comment in special paragraph clinical data and surveillance in this group of patients.

Thank you for this comment. This information is added in the maintext (page 7)

Please add to abstract: Grade F3 fibrosis (Metavir) is associated with high risk ov HCC in NAFDL, HBV and HCV patients.

Thank you for this comment. This information is added to abstract (page 3).

4) HCC prevalence in Wilson's disease is lower than in other inherited disease, please add 1 or 2 sentences in text.

Thank you for this comment. This information is added to the text. (Page 10)



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5) Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas is not described in review, please add one special paragraph

Thank you for this comment. This information is added in a new special paragraph in the maintext (page 11).

6) Chapter Alpha-Fetoprotein: Please emphasize the role of AFP dynamics for identifying of HCC patients.

Thank you for this comment. This information is now added to the maintext (page 12).

7) Please report in short paragraph differences in the clinical course and management of HCC in non-cirrhotic liver compared to cirrhotic HCC patients.

Thank you for this comment. This information is presented in the keypoints section (page 2).

I recommend to publish this interesting review for publication in World Journal of Hepatology after accpetation of major changes.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

- The same title



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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer’s code: 03253490

Reviewer’s country: Turkey

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-09-03

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Desai et al. discusses the epidemiology, risk factors, clinical features, diagnosis and management of HCC in non-cirrhotic patients in this review. The idea is smart and the review is very usefull.

Some issues raised: 1-Hepatitis B, Hepatitis C parts in risk factors section



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should be more detailed (active viral replication, inactive HBV carriers, effects of HBV and HCV treatments etc.)

Thank you for this comment. This information is present on page 6 and 7.

2-NAFLD part in risk factors section is too short and should be more detailed (pathogenesis, DM, comorbidities, obesity etc.)

Thank you for this comment. This section is expanded to include more information on NAFLD. (page 5)

3-New studies about micro RNAs, iron metabolism (ferroptosis etc.) should be added to this review.

Thank you for this comment. A new section on microRNAs is added on page 21.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 41621

Title: Hepatocellular Carcinoma in Non-Cirrhotic Liver: A Comprehensive Review.

Reviewer’s code: 03476715

Reviewer’s country: China

Science editor: Fang-Fang Ji

Date sent for review: 2018-08-24

Date reviewed: 2018-09-04

Review time: 10 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this comprehensive review, the authors summarized the pathology, epidemiology, diagnosis, treatments and prognosis of HCC in non-cirrhotic patients. The manuscript was well-written and very informative. However, I think the authors should focus on the distinctive features of HCC in non-cirrhotic liver and provide more information of the



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differences between non-cirrhotic and cirrhotic patients,. Moreover, NAFLD has been suggested to be a major cause of HCC in non-cirrhotic patients, the pathological and the prognostic features in this populations need extensive description.

Thank you for this comment. Information on NAFLD is expanded to include more studies and information on this important topic and role it plays in HCC (page 5 and 6).

The differences between non cirrhotic and cirrhotic are summarized in the keypoints section (page 2).

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