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Research Article

HCV seropositivity and breast cancer in Egyptian population, is there a link?

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Abstract

Background: HCV is a significant contributor to mortality associated with liver-related conditions globally. In addition to its known association with extrahepatic cancers, such as lung and pancreatic cancer, this research aimed to investigate the potential correlation between HCV seropositivity and the occurrence of breast cancer. Furthermore, the study aimed to assess the impact of HCV infection on survival rates within the Egyptian population. **Methods:** This retrospective case-control study involved of 938 female patients diagnosed with breast cancer, who were categorized into cancer groups. Their HCV seropositivity status was then compared to a control group consisting of 1251 female individuals. HCV seropozitivity was determined by the presence of HCV antibodies in the blood samples of the subjects. The study compared the characteristics of breast cancer patients who tested positive for HCV antibodies with those who tested negative, focusing on factors such as TNM staging, histological grading, and survival outcomes. **Results:** 938 female breast cancer cases (with a mean age of 50.7 years) were compared to 1251 female controls (with a mean age of 52.2 years). HCV seropositivity among breast cancer cases was notably higher than that among controls (8.1% vs. 5.7%) [OR = 1.47, P = 0.031]. Additionally, this study revealed a non-significant increase in survival rates among breast cancer seropositive patients compared to seronegative [HR = 0.79, P = 0.513]. **Conclusion:** HCV sero-positivity was found to be associated with elevated risk of developing breast cancer; however, it did not demonstrate a significant impact on survival in breast cancer patients.

Keywords: HCV, sero-positivity, breast cancer, survival

Abbreviations:

- **HCV:** Hepatitis C virus.
- **HR:** hazard ratio.
- **P:** probability.
- **OR:** odds ratio.
- **CI:** confidence interval.

Introduction

Hepatitis C virus (HCV) is a prevalent chronic illness worldwide, and its incidence is quite high [1]. Egypt, in particular, had the highest prevalence of HCV infection in the past, largely due to the widespread occurrence of schistosomiasis and the extensive use of unsafe intravenous injections for its treatment between the 1950s and 1980s [2]

Numerous studies have established a connection between chronic HCV infection and a heightened risk of various non-hepatic cancers, such as thyroid and kidney cancer [3,4]

Breast cancer is the most prevalent form of cancer among women, impacting approximately 1.7 million women globally and resulting in 521,900 deaths in the year 2012 [5,6]. In Egypt, breast cancer constitutes 18.9% of all cancer cases, with a rate of 49.6 cases per 100,000 individuals. It affects 32.04% of female cases and 2.2% of male cases [7,8]

The objective of this study was twofold: first, to investigate the potential association between HCV sero-positivity and the incidence of breast cancer within the Egyptian population, and

second, to examine whether HCV sero-positivity had any impact on the prognosis of individuals diagnosed with breast cancer.

Patients and Methods

- **Study Design:** This study utilized a retrospective case-control design.
- **Study Settings**: The research was conducted at the department of oncology, Beni Suef University Hospital, from January 1st, 2017, to December 31st, 2021.
- **Study Groups:** The research group included 938 out of 1029 female patients who had a confirmed diagnosis of breast cancer. Excluding 91 cases with unclear HCV sero-condition, the remaining eligible patients were assessed for HCV sero-prevelance. Subsequently, 126 patients who had dropped out of follow-up prior to initiating cancer therapy were excluded. The remaining 812 patients were divided into two subgroups: HCV seropositive (67 cases) and HCV seronegative (745 cases). **The control group** consisted of 1251 female individuals who were randomly selected from the attendees of Beni-Suef University Hospital, excluding those in the cancer department during the same time frame.
- **Methods:** Relevant information was extracted from the hospital's medical record system for all confirmed female breast cancer patients. This included age, initial tumor stage information according to TNM classification, tumor grade, histopathological type, anti-HCV serological status at diagnosis, survival duration, date and status at the last hospital visit, and other pertinent data. HCV sero-pozitivity was defined based on the presence of positive HCV antibodies in the subjects. The study aimed to compare the prevalence of HCV sero-positivity between the research group and the control group.

The HCV sero-positive and sero-negative subgroups were compared in terms of several variables, including age, initial TNM staging, histological grading, histopathological type, and cancer survival.
The age distribution between the HCV sero-positive and sero-negative subgroups was analyzed and compared.

The initial TNM staging, which provides information about the extent and spread of the tumor, was evaluated for both the HCV seropositive and seronegative subgroups and their differences were examined.

Histological grading, which assesses the cellular characteristics of the tumor, was compared between the HCV seropositive and seronegative subgroups.

The histopathological type of breast cancer was documented for both subgroups, and any variations between HCV seropositive and seronegative patients were investigated.
Furthermore, the study investigated the impact of HCV sero-positivity on cancer survival, comparing the survival rates between the two subgroups.

TNM staging [9]:
Indeed, TNM staging is considered one of the key factors in predicting survival outcomes for cancer patients. TNM staging provides valuable information about the size and extent of the primary tumor (T), the involvement of nearby lymph nodes (N), and the presence or absence of distant metastasis (M). By categorizing tumors into different stages, TNM staging helps to assess the prognosis and guide treatment decisions for cancer patients.

Histological grading [10]:
Histological grading is a cost-effective and straightforward method used to assess the behavior and prognosis of tumors. By examining the cellular characteristics and patterns of tumor growth, histological grading provides valuable information about the aggressiveness and potential outcome of the tumor.

In this study, data collection and statistical analysis were conducted up until 2022, ensuring that the most recent and comprehensive information was in-corporated into the research findings. By including data from a recent time-frame, the study aimed to provide up-to-date in-sights into the relationship between HCV sero-positivity, histological grading, and cancer prognosis in the Egyptian population.

Statistical analysis:
The data analysis was performed using SPSS version 20 software (IBM, Armonk, NY). The

collected data were procesed, tabulated, and presented visually using charts & graphs.
For continous variables that followed a normal distribution, the mean and standard deviation were calculated. To compare categorical data, the Chi-square test was employed, while an independent t-test was used for comparing quantitative data.

In order to assess the relationship between HCV sero-positivity and the development of cancer, odds ratios (ORs) and 95% confidence intervals (CIs) were computed.
The Cox-regression analysis tool was utilized to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for examining the association between HCV sero-positivity and survival in extra-hepatic cancers.

For the survival duration analysis, the Kaplan-Meier survival analysis tool was employed.
A p-value of less than 0.05 was considered statistically significant in determining the results.

Ethical consideration:
This study has obtained ethical approval from the Ethics Committee at Minia University's Faculty of Medicine. Prior to participation, the subjects or their legal representatives were provided with information about the study's objectives, implications, and the significance of maintaining data confidentiality. The protocol and implementation of the study adhere to the ethical criteria outlined in the Helsinki Declaration of 1975.

Results
In this retrospective case-control study, 938 female breast cancer patients were compared to 1251 female controls in terms of HCV seropositivity. Among the research group, 812 cases were examined for the relationship between HCV seropositivity and survival.
The research group participants were found to be significantly younger than the controls, with mean ages of 50.7 years and 52.2 years, respectively (p = 0.02).

The proportion of HCV seropositive patients in the research group was significantly higher compared to the control group, with rates of 8.1% and 5.7%, respectively (odds ratio [OR] = 1.47, 95% confidence interval [CI]: 1.05-2.05, p = 0.031) (Table 1).

No statistically significant differences were observed in cancer histological grading and TNM staging between HCV seropositive and seronegative breast cancer participants (Table 2).
Regarding cancer survival, HCV seropositive breast cancer individuals showed a non-significant increase in survival compared to seronegatives (hazard ratio [HR] = 0.79, 95% CI: 0.39-1.61, p = 0.513) (Table 3).
The survival duration was insignificantly longer in HCV seropositive breast cancer subjects (52 months) compared to seronegatives (50.1 months) (p = 0.51) (Table 4 and Figure 1).
(Note: Tables and figures mentioned are not provided in the text and are assumed to be present in the original research study.)

Table 1. HCV antibody seroprevalence among the research group compared to that of control group:

HCV positive in the research group (938 subjects), n(%)	HCV positive in the control group (1251 subjects), n(%)	OR (95%CI) ‡	P value#
76 (8.1)	71(5.7)	1.47 (1.05–2.05)	0.031*

 # P value is obtained by Chi square test.
****P value is considered significant "P < 0.05".***

Table 2: Clinicopathological criteria of breast cancer in relation to HCV serocondition:

		HCV serocondition		P value
		Positive	Negative	
TNM stage	Early	46.3	44.7	0.804
	Late	53.7	55.3	
Hist. grade	I	1.5	1.7	0.983
	II	89.5	88.3	
	III	9	9.8	
	IV	0	0.1	

P value is considered significant "P < 0.05".

Table 3: Association between HCV serocondition and survival among subjects in breast cancer group:

Number of subjects		N	HCV +ve n (%)	HCV –ve n (%)	HR# (95% CI)	P value*
812	Died	111	8 (7.2)	103 (92.8)	0.79 (0.39−1.61)	0.51
	Survived	701	59 (8.4)	642 (91.6)	1	

**P value is obtained by Chi square test.*
#HR: Hazard ratio.

Table 4: Mean survival duration (in months) in HCV seropositive and seronegative subjects in breast cancer group:

HCV seropositive Mean survival duration (month)	HCV seronegative Mean survival duration (month)	P value#
52.0	**50.1**	**0.51**

#P value was obtained by log tank (Mantle-Cox) test.

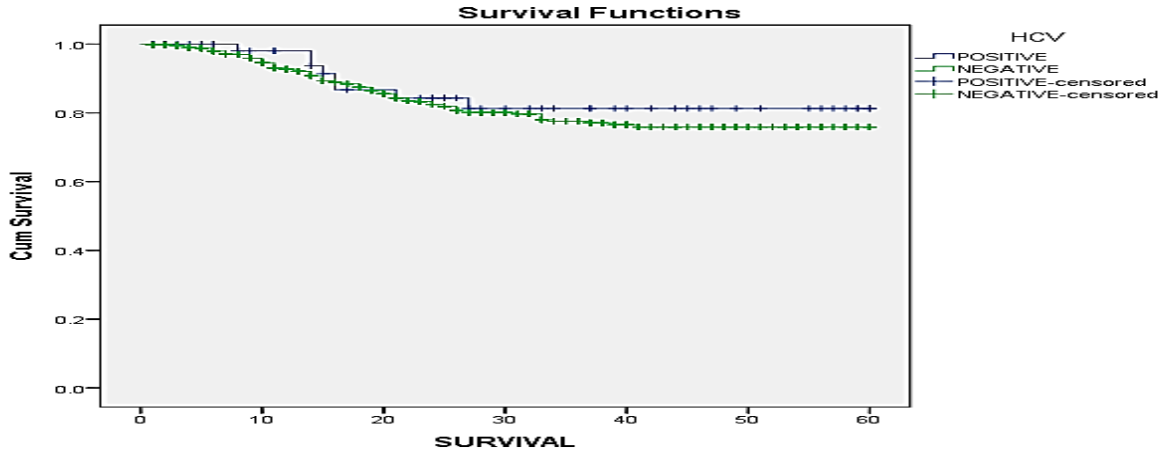

Figure (1): Kaplan Meier survival curve for breast cancer subjects.

Discussion

HCV (hepatitis C virus) is a prevalent blood-borne virus [11,12]. Cancer ranks among the top causes of mortality in the United States[13]. Infectious infections are responsible for approximately 15% of all human malignancies [14]

The aim of our study was to investigate the prevalence of HCV antibodies in breast cancer patients and determine if HCV sero-positivity affects breast cancer survival in the Egyptian population.

Our research revealed that breast cancer patients had a significantly higher proportion of HCV sero-positivity compared to controls [8.1% vs. 5.7%, odds ratio (OR) = 1.47, 95% confidence interval (CI): 1.05-2.05, p = 0.031] (Table 1). These findings are consistent with a study by Hussein et al., (2021), which reported a higher prevalence of HCV sero-positivity in breast cancer patients compared to non-cancer individuals [21.7% vs. 10.3%, p = 0.0027] [15]. Similarly, Cheng et al. (2022) found a strong link between HCV infection and the development of breast cancer in individuals aged 49 years [hazard ratio (HR) = 2.19, 95% CI: 1.097-4.384] [16]. However, Wang et al., (2019) reported a lower risk of breast cancer associated with HCV infection [HR = 0.87, 95% CI: 0.77-0.97] [17]. Another study by Liu et al., (2019) found no significant difference in HCV prevalence between breast cancer patients and controls [0.5% vs. 0.65%, OR = 0.76, 95% CI: 0.48-1.21, p = 0.244] [18]

Regarding cancer staging and grading, our study did not find any significant differences between HCV sero-positive and sero-negative breast cancer participants (Table 2). This is consistant with the findings of Hussein et al., (2021), who reported no association between HCV serology status and breast cancer staging and grading [15]. Additionally, Allison et al., (2015) found no significant differences in grade and stage of cancer between individuals with chronic HCV and controls [19]

In terms of survival, our study showed that there was no substantial difference in survival length between HCV sero-positive and sero-negative breast cancer patients [52 months vs. 50.1 months, HR = 0.79, 95% CI: 0.39-1.61, p = 0.51]. Hussein et al., (2021) also found no statistically significant difference in survival between HCV sero-positive and sero-negative breast cancer participants [HR = 1.65, 95% CI: 0.74-3.21, p = 0.25] [15]. However, Allison et al. (2015) reported a reduced risk of breast cancer in HCV-infected women compared to controls [relative risk (RR) = 0.42, 95% CI: 0.41-0.43, p = 0.02] [19]. Discrepancies among these studies could be attributed to variations in geographical areas, endemicity of HCV infection, age, gender, and race of the study subjects. Liu et al., (2019) suggested that the association between HCV infection and cancer incidence is particularly notable in areas with endemic HCV infection [18]

- **Limitations of this study:**

Indeed, our conclusions are valid and highlight the limitations of the study. A retrospective case-control design has inherent limitations in establishing a definitive causal association. The reliance on medical records may introduce biases, and the inability to investigate environmental factors, occupational exposures, and comorbidities limits the comprehensive understanding of the relationship between HCV infection and breast cancer. The limited sample size and the single-center nature of the study also restrict the generalizability of the findings. To gain a better understanding and clarify the association between HCV infection and breast cancer, as well as its impact on survival and prognosis, larger multicentric prospective studies that control for relevant risk factors are warranted. These studies would provide more robust evidence and help establish a clearer understanding of the relationship between HCV seropositivity and breast cancer in the Egyptian population.

Conclusion:

Our study yielded significant evidence supporting a positive association between HCV sero-positivity and the development of breast cancer in the Egyptian population. However, it is important to note that our findings did not demonstrate a significant impact of HCV sero-positivity on patient survival in this context. Further research should aim to explore the influence of other environmental variables and co-morbidities on survival outcomes in breast cancer patients with HCV infection. By investigating these factors, future studies can provide a more comprehensive understanding of the complex interplay between HCV infection,

breast cancer development, and patient prognosis.

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Conflicts of interest: No conflicts of interest.

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