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Factors affecting the survival and long-term outcomes in patients undergoing hepatic resection for hepatocellular carcinoma: A narrative review

Mohammed Abdulla Banama [1]*

[1] *Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates.*

Abstract

Background: Hepatocellular carcinoma is common cancer with high morbidity and mortality. While different treatment modalities such as hepatic resection or liver transplant are available, the risk of recurrence may still prevail. However, the possibility of recurrence and survival rate are affected by different prognostic factors that have been explored in various research studies, but the findings are not synthesized and reviewed collectively. Hence, this narrative review was carried out to review the existing literature on determinants of cancer recurrence and survival rate in patients diagnosed with hepatocellular carcinoma.

Methods: A literature review was carried out using databases such as PubMed and CINAHL. The main outcomes were cancer recurrence and survival rate among patients with hepatocellular carcinoma. All studies conducted between 1990 to 2022 were included, and after searching the articles, finally, 14 research studies were reviewed to extract the data on the author, study year, the country where the study was conducted, five or ten or overall survival rate, and key findings on factors associated with recurrence and survival.

Results: The findings revealed that survival rates varied in different populations ranging between 32% to 65.5%. Similarly, the recurrence rate also differed across countries ranging between 29% to 63%. The multivariate analyses in the respective studies revealed the most common predictors for poor survival or recurrence were the presence of symptoms and vascular invasion, type of treatment followed by patient's age, use of alcohol, the large size of the tumor, poor liver function tests, elevated levels of alpha-fetoprotein, multiple tumors, and positive margins on the microscope. Patients who underwent surgical resection as opposed to other treatment modalities, such as radiofrequency and transarterial oily chemoembolization, had poor survival rate and increased risk of recurrence.

Conclusion: The review findings provide useful insights into the determinants of recurrence and survival among patients undergoing hepatic resection for hepatocellular carcinoma. The majority of the studies identified the type of treatment and presence of symptoms, and vascular invasion as the common prognostic factors in these patients. These findings may be useful in determining the treatment strategies and post-operative schedules to manage these patients effectively. In addition, these findings may also be helpful in counseling family members and making informed decisions for them.

Keywords: Hepatocellular carcinoma; survival; recurrence; factors; narrative review.

*Mohammed Abdulla Banama - Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates; Email: Mabanama@dha.gov.ae. Orcid.org/0000-0002-4841-7644 .

1. Introduction

Hepatocellular carcinoma is considered the sixth most widely prevalent cancer due to its poor prognosis, with approximately 626,000 incident cases and 600,000 fatalities every year worldwide[1, 2]. It is the third most common cause of mortality across the globe[2]. With the rising trend of chronic hepatitis viral infections and improved survival in cirrhotic patients, the number of hepatocellular carcinomas is rising [3-5]. Besides, the rising trend is also attributed to an increase in diagnostic and detection techniques and an increase in the immigrant population from countries with a higher burden of hepatocellular carcinoma[3-5].

Early diagnosis, proper staging, and timely treatment are important in determining the prognosis of these patients. Surgical resection with hepatic resection, liver transplantation, percutaneous & locoregional therapy, cytotoxic chemotherapy, and hormonal therapy are considered the treatment modmodality[6, 7]. However, hepatic resection is not offered to all patients, rather, it is saved for patients with optimal liver function and well-defined tumors with restricted hepatic resection[6]. Otherwise, liver transplantation is the only choice among patients with inadequate liver function or in patients with non-resectable masses[6, 7]. However, the recurrence of hepatocellular carcinoma is possible, especially among patients with cirrhosis[8]. Therefore, prognostic analysis and assessment of factors are necessary to identify the determinants of recurrence and survival in such patients. Many factors determine the survival and recurrence rate in patients with hepatocellular carcinoma. These factors can be helpful for clinicians and hepatologists to make treatment or palliative decisions and counsel families after undertaking prognostic analysis.

The existing literature provides insights into the factors and determinants of recurrence and five and ten-year survival in these patients. This narrative review was carried out to review the existing literature on determinants of cancer recurrence and survival rate in patients diagnosed with hepatocellular carcinoma. The findings of this review can be helpful for researchers and physicians to make informed decisions about deciding the future treatment pathways for these types of patients.

2. Material and Methods

A review of the literature was carried out using databases such as PubMed and CINHAL. The main outcomes were recurrence of cancer and survival rate among patients with hepatocellular carcinoma. Key search terms such as “factors OR determinants” AND “recurrence”, “hepatocellular carcinoma” OR “hepatocellular cancer” AND “survival” OR “mortality” were used to retrieve the articles. Studies that investigated factors of recurrence or survival in patients with hepatocellular carcinoma were included. In addition, any primary study published in the English language in a peer-reviewed journal was found to be

eligible for this review. All qualitative studies or experimental studies were excluded as they did not serve the purpose of the review. We included all studies conducted between 1990 to 2022 to have a wide range of articles from diverse regions and countries. All articles were imported into Endnote software, and full texts of eligible articles were reviewed using eligibility criteria. Besides, the appropriate and relevant references of the suitable articles were reviewed to avoid missing any germane study. The data were extracted for variables such as author, study year, the country where the study was conducted, five or ten or overall survival rate, and key findings on factors associated with recurrence and survival.

3. Results

Altogether 14 studies were included in this narrative review, and these studies were conducted on patients diagnosed with hepatocellular carcinoma. The included studies were conducted in different countries such as India, Singapore, South Korea, and the United States of America. For example, a study carried out by Vauthey et al. on 106 patients found that overall 5-year and 10-year survival rates were 41% and 32%, respectively, following the resection in patients with hepatocellular carcinoma[9]. The greater survival rate factors included the absence of any vascular invasion and symptoms. For example, the survival rate was 69% among patients with the absence of vascular invasion and 28% with the presence of vascular invasion. Similarly, the 5-year survival was 66% in symptomatic patients compared to 38% in asymptomatic patients[9]. Patients with negative margins had 46% survival when compared to patients with positive margins. Likewise, the tumor size also predicted the survival, and patients with small tumors of less than and equal to 5cm had a 75% survival rate than patients with larger tumors [9]. However, these findings were significant in the univariate analysis, and multivariate analysis found the absence of vascular invasion is an important predictor of survival in these patients[9].

These findings are consistent with a study undertaken by Shah et al. on 56 patients in Canada[10]. The authors found that recurrence occurred in 38% of the patients, and their median survival rate was 27 months[10]. Multivariate analysis revealed vascular invasion and positive margins as essential and statistically significant factors of recurrence in the final model (P-value <0.05)[10]. Similarly, another study conducted by Montorsi et al. on 98 patients found that intrahepatic recurrence was predicted by the type of treatment[11]. For example, patients undergoing radiofrequency had higher intrahepatic recurrence (53%) than after having resection (30%) as a treatment option, and the results were statistically significant (p-value:0.018)[11]. The findings of the multivariate analysis revealed that the level of alpha-fetoprotein, the cause of cirrhosis, and the type of treatment were important predictors of intrahepatic recurrence[11]. However, the level of alpha-fetoprotein was an important predictor of survival in these patients[11]. Okada et al. conducted a study on 98 patients to assess the survival and recurrence rate in

patients with hepatocellular carcinoma[12]. The authors found that no alcohol use, DNA diploidy, and no vascular invasion were found to be good prognostic factors for survival[12].

Another study conducted by Chiappa et al. on 51 patients found that tumor recurrence occurred in 45% of the patients, with 52% of the recurrence occurring within a year and 96% of the recurrence occurring within three years[13]. These findings demonstrated a higher rate of recurrence in these patients with a low survival rate[13]. The important factors of recurrence were vascular invasion and the presence of symptoms[13]. Likewise, another study conducted by Poon et al. on 240 patients found that one year, three-year, and five-year survival rate was 65.5%, 34.9%, and 19.7%, respectively[14]. Patients who underwent transarterial oily chemoembolization had poor survival rate than patients undergoing resection[14]. In multivariate analysis, the authors found that grading, liver function status as determined by levels of albumin (≤40g/L), and history of numerous recurrent tumors were found to be associated with recurrence of cancer[14].

Tabrizian et al. conducted a research study on 661 patients in the USA to determine the factors associated with survival post recurrence of hepatocellular carcinoma[15]. The study results showed that 54% of the patients developed recurrence after about 22 months from primary resection of cancer[15]. Factors such as alpha-fetoprotein levels greater than 100gg/ml, size of tumor greater than 3cm, staging, and type of treatment were predictors of survival in these patients. Similarly, research conducted by Jun et al. on 743 patients in South Korea had similar findings[16]. The authors found that age of more than 50 years, tumor size of less than 6cm, good liver function tests, absence of vascular invasion and no distant metastasis, and unipolar tumor type were predictors of survival in these patients[16]. Likewise, Bhanu et al. conducted the study in India, and the authors found that the local recurrence rate was 29%. On average, the recurrence occurred after eight months of original resection[17]. Respectively, the five-year disease survival and overall study survival were 26% and 32% [17]. The factors of poor survival included presence of vascular invasion (P-value: 0.047), age less than 55 years (P-value: 0.021) and increased levels of alpha-fetoprotein (P-value: 0.041) [17] .

Kim et al. undertook a study in South Korea on 170 patients and found that 30.5% of the patients survived beyond ten years, and the overall 10-year survival rate was 30.6%[18]. The multivariate analysis findings illustrated that satellite nodule, elevated levels of ICGR15, positive HBeAg, and recurrence of tumor were negatively associated with the ten-year disease-free survival rate[18]. The presence of HBeAg was also negatively associated with overall survival [18]. Similarly, Linn et al. carried out a retrospective review on 600 patients in Singapore[19]. The results demonstrated that 40.7% of the patients had recurrence within ten years, with an actual ten-year survival rate of 31.5%[19]. The final

model revealed that age of more than 65 years (P-value: <0.001) and diagnosis of cirrhosis (P-value: 0.005) were found to be negatively associated with actual ten-year overall survival[19]. Lang et al. evaluated prognostic factors in 83 patients in Germany[20]. Tumor recurrence occurred in 63% of the patients, and factors such as vascular invasion and tumor grading and staging were found to predict survival rate and recurrence in these patients[20].

Recently a study conducted on 1424 patients in China demonstrated that almost 48% of the patient's developed recurrence after 54 months[21]. The risk factors for the recurrence were cirrhosis, higher levels of alpha-fetoprotein levels (>400ug/L), the size of the tumor (>5cm), microvascular invasion, numerous tumors, and intraoperative blood transfusion[21]. Another study by Worns et al. found that recurrence occurred in 57% of the patients enrolled in the study and five-year survival rate was 31% in the patients[22]. Factors such as viral hepatitis and vascular invasion decreased the survival rate. In addition, use of tobacco was also associated with decreased survival rate in these patients[22]. Andreou et al. conducted a study on 539 patients and the authors found the five-year survival rate was 40%[23]. The authors found that higher levels of alpha feto protein, tumor size of more than 5cm, major vascular invasion, and extrahepatic metastases, and positive surgical margins reduced the survival rate in patients[23].

4. Conclusion and future implications of findings

The review findings provide valuable insights into the determinants of recurrence and survival among patients undergoing hepatic resection for hepatocellular carcinoma. Overall, the findings demonstrated that type of treatment is considered an essential determinant of recurrence and survival. More precisely, patients undergoing surgical resection as opposed to other treatment modalities such as radiofrequency and transarterial oily chemoembolization had better survival and lower rates of recurrence. In addition, poor liver function, size of the tumor, presence of vascular invasion, use of alcohol, positive tumor margins on microscopy, and history of recurrent tumors were found to be determinants of recurrence and poor survival. Among all of these factors, the majority of the studies identified the type of treatment and presence of symptoms and vascular invasion as the common prognostic factors in these patients in their multivariate analysis. This was followed by other factors such as age, use of alcohol, size of the tumor, presence of HBeAg, staging, and grading. The narrative of the findings may be useful in determining the treatment strategies and post-operative schedules to effectively manage these patients. In addition, these findings may also be helpful in counseling family members and making informed decisions for them.

5. Declarations

5.1 Conflict of Interest Statement

The authors have no conflict of interests to declare.

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