Cohort Study

Effects of surgery, chemotherapy, and radiation on hepatocellular carcinoma patients: A SEER-based study

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a major global health issue, accounting for 75%–85% of primary liver cancer cases. HCC has huge molecular heterogeneity, and the treatment varies among the patients. The aim of this study is to assess the effect of surgery, chemotherapy, and radiation on the mortality risk in hepatocellular carcinoma (HCC) patients.

Methods: A retrospective cohort study, obtaining HCC patients’ data from the Surveillance, Epidemiology, and End Results (SEER) database. The analyses were conducted using the SPSS software. We investigated the effect of surgery, chemotherapy, and radiation on the mortality risk factors using the Kaplan–Meier and the Cox regression tests in the univariate and multivariate analyses.

Results: A total of 68,270 HCC patients, of whom 56,347 patients died, were analyzed. In patients who performed surgery, the mortality risk was higher in patients aged ≥50 years, Black, single, and widowed, regional and distant stages, and grades II, III, and IV (HR, 1.143), (HR, 1.057), and (HR, 1.095), (HR, 1.284), (HR, 1.341), (HR, 2.291), (HR, 1.125), (HR, 1.711), (HR, 1.894) respectively. In patients who received chemotherapy, the risk was higher in Black (HR, 1.195), widowed (HR, 1.143), and (HR, 1.479), (HR, 1.688) respectively. In patients who received beam radiation, the risk was higher in Black (HR, 1.143), (HR, 1.095), (HR, 1.284), (HR, 1.341), (HR, 2.439), (HR, 1.711), (HR, 1.894) respectively. In patients who received chemotherapy, the risk was higher in Black (HR, 1.195), widowed (HR, 1.143), (HR, 1.479), and (HR, 1.688) respectively. In patients who received chemotherapy, the risk was higher in Black (HR, 1.195), widowed (HR, 1.143), (HR, 1.479), and (HR, 1.688) respectively. In patients who received chemotherapy, the risk was higher in Black (HR, 1.195), widowed (HR, 1.143), (HR, 1.479), and (HR, 1.688) respectively.

Conclusion: In HCC patients, Black, widowed, regional, and distant stages, grades III and IV had higher mortality risks in several treatment options. In patients who underwent surgery, ≥50 years and grade II also had a higher risk. We recommend future research to assess the radiation sequence with surgery.

1. Introduction

Hepatocellular carcinoma (HCC) is a common global malignancy with considerable morbidity and mortality [1,2]. HCC is responsible for 75%–85% of primary liver cancer cases, and primary liver cancer is globally the sixth most commonly diagnosed cancer and the third leading cause of cancer death [3]. Various sociodemographic features were associated with HCC, mainly in patients with cirrhosis [4]. For example, the incidence increases with advancing age in all populations [5]. Moreover, both incidence and mortality rates are 2–3 times higher among males in most world regions. This is possibly due to a clustering of risk factors among males and the differences in the sex hormones [4,6].

Very early or early stage HCC (BCLC 0, A) patients are eligible for curative surgical treatment and locoregional ablation, yielding survival times of >5 years. Intermediate stage (BCLC B) patients receive transarterial chemoembolization with <2–5 survival years. Radiation therapy can be used solely or as a crucial element of combined therapy [7]. Unfortunately, the prognosis of HCC is poor worldwide [8].

HCC is known for its huge molecular heterogeneity [9]. Also, the treatment options differ among patients and greatly depend on the disease stage [10]. Therefore, it is important to study the effect of...
different factors according to the treatment. So, this study aims to assess the impact of several variables regarding different treatment options (surgery, chemotherapy, radiation, and radiation sequence with surgery) on the mortality risk in patients with HCC.

2. Methods

2.1. Study design

We followed the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)” guidelines to conduct this retrospective cohort study [11]. We also followed the Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) criteria [12]. We registered the study protocol in Research Registry (UIN: researchregistry7087) [13].

2.2. Ethical approval

SEER data are publicly available and anonymized. So, the ethical approval was waived.

2.3. Study population and data collection

Our sample included all available patients’ data diagnosed with hepatocellular carcinoma registered in the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2016. SEER database involves data of cancer patients in the United States and makes the data accessible upon request. We grouped patients according to the treatment received; patients with or without surgery, patients with or without chemotherapy, and patients without radiotherapy. The follow-up period was until the end of 2016 or until death. We collected data concerning age, sex, marital status (single, married, divorced, separated, and widowed), race (White, Black, and others (American Indian/AK Native, Asian/Pacific Islander)), stage of the disease (localized, regional, and distant), grade (Grade I; well-differentiated, Grade II moderately differentiated, Grade III; poorly differentiated, Grade IV; undifferentiated; anaplastic, and unknown), chemotherapy (yes or no), surgery (yes or no), radiation (beam, others, and none), radiation sequence with surgery (after surgery, intraoperative, prior to surgery, no radiation or surgery, radiation before and after, and surgery before and after). Our primary outcomes are to identify survival months and mortality risk factors among different treatment groups.

2.4. Statistical analysis

We conducted the analysis using SPSS software for windows (version 26.0). We conducted univariate and multivariate analyses using the Kaplan-Meyer test and the Cox regression test. These analyses were conducted according to a separate comparison for each of surgery, chemotherapy, radiation, and radiation sequence with surgery. We presented the data as median (months) and 95% confidence interval (CI), and hazard ratio and 95% CI data of the univariate and multivariate analyses, respectively. We considered any analysis to be significant when the P-value was less than 0.05.

3. Results

3.1. Characteristics of the study population

We reviewed data of 68270 hepatocellular carcinoma patients, 56347 of them were dead. The mean age was 59.88 for the living patients and 63.27 for the dead, with a total mean age of 62.68 years. The majority of all patients were males (52342; 76.7%), and were White (45137; 66.1%), 37407 (54.8%) of the patients were married, 34064 (49.9%) were diagnosed at a localized disease stage, 10070 (14.8%) had grade II, and 43969 (64.4%) had an unknown grade. 24258 (35.5%) and 16456 (24.1%) received chemotherapy and underwent surgery, respectively. On the other hand, 63763 (93.4%) patients did not receive radiation therapy, and 67673 (99.1%) had no radiation therapy or surgery. Table 1 shows the details of the study population’s characteristics.

3.2. Univariate and multivariate analyses according to surgery performance comparison (Table 2)

3.2.1. Univariate analysis of patients who performed surgery

The median overall survival was equal in males and females (20 months) and in White and Black races (20 months), but higher in other races (21 months). According to the marital status, the median overall survival was the highest in married patients (21 months), equal in separated and divorced (20 months), and the lowest in single and widowed (19 months). Staging-wise, the localized stage had the longest median survival (24 months), followed by the regional (15 months), and the least with the distant (7 months). The higher the grade, the shorter the median survival; grade I had a median survival of 28 months, grade II had 23 months median survival, grade III had 14 months median survival, and the shortest survival was with grade IV (12 months).

3.2.2. Univariate analysis of patients who did not perform surgery

Generally, the median overall survival was markedly lower in patients who did not perform surgery than those who performed it. The highest median survival reached 6 months only, which occurred only Table 1

| Variables              | Alive (11923) | Dead (56347) | Total (68270) |
|------------------------|---------------|--------------|---------------|
| Age                    | 59.88 (10.545) | 63.27 (11.661) | 62.68 (11.545) |
| Male                   | 11209 (94%)   | 52554 (93.3%) | 63763 (93.4%) |
| Female                 | 6124 (66%)    | 30793 (56.7%) | 37407 (54.8%) |
| Race                   | 7725 (64.8%)  | 37412 (66.4%) | 45137 (66.1%) |
| White                  | 7145 (60%)    | 37412 (66.4%) | 44012 (64.5%) |
| Black                  | 1214 (10.2%)  | 7931 (14.1%)  | 9145 (13.4%)  |
| Others                 | 6946 (56%)    | 37471 (66.5%) | 43969 (64.4%) |
| Grade                  | 1923 (16.1%)  | 6070 (10.8%)  | 7993 (11.7%)  |
| II                     | 2687 (22.5%)  | 7383 (13.1%)  | 10070 (14.8%) |
| III                    | 754 (6.3%)    | 4885 (8.6%)   | 5612 (8.2%)   |
| IV                     | 61 (0.5%)     | 565 (1%)      | 626 (0.9%)    |
| Unknown                | 6496 (54.5%)  | 37471 (66.5%) | 43969 (64.4%) |
| Chemotherapy           | 5332 (44.7%)  | 18926 (33.6%) | 24258 (35.5%) |
| No                     | 6591 (55.3%)  | 37421 (66.4%) | 44012 (64.5%) |
| Surgery                | 6728 (56.4%)  | 9728 (17.3%)  | 16456 (24.1%) |
| Yes                    | 5195 (43.6%)  | 46619 (82.7%) | 51814 (75.9%) |
| Radiation              | 211 (1.8%)    | 2455 (4.4%)   | 2666 (3.9%)   |
| Beam                   | 503 (4.2%)    | 1388 (2.4%)   | 1841 (2.7%)   |
| Others                 | 11209 (94%)   | 52554 (93.3%) | 63763 (93.4%) |
| Radiation sequence with surgery | 49 (0.4%) | 321 (0.6%) | 370 (0.5%) |
| After surgery          | 9 (0.1%)      | 21 (0%)       | 30 (0%)       |
| Intraoperative         | 98 (0.8%)     | 89 (0.2%)     | 187 (0.3%)    |
| Prior to surgery       | 11763 (98.7%) | 55910 (99.2%) | 67673 (99.1%) |
| Radiation before and after | 3 (0%)   | 5 (0%)       | 8 (0%)        |
| Surgery before and after | 1 (0%)    | 1 (0%)       | 2 (0%)        |
with grade I patients and patients with a localized stage. On the other hand, the lowest median survival occurred with patients having a distant stage (1 month). The majority of the different variables had a median survival of 3 months.

3.2.3. Multivariate analysis of patients who performed surgery
The mortality risk was significantly higher in patients aged ≥50 years (HR, 1.143; 95% CI, 1.074–1.217) than patients <50 years. The risk was significantly lower in females than in males (HR, 0.94; 95% CI, 0.897–0.985).

Races other than Black had a significantly lower risk than White patients (HR, 0.856; 95% CI, 0.815–0.899). The mortality risk was significantly higher in single patients (HR, 1.064; 95% CI, 1.035–1.158) and widowed patients (HR, 1.284; 95% CI, 1.192–1.384) than married patients. Other details are provided in Table 2.

3.2.4. Multivariate analysis of patients who did not perform surgery
The mortality risk was significantly lower in females than in males (HR, 0.94; 95% CI, 0.894–0.985). The mortality risk was significantly higher in patients aged ≥50 years (HR, 1.143; 95% CI, 1.074–1.217) than patients <50 years. Other details are provided in Table 2.

3.3. Univariate and multivariate analyses according to chemotherapy comparison (Table 3)

3.3.1. Univariate analysis of patients who received chemotherapy
Patients with ≥50 years lived longer than patients <50 years (median 10 months and 8 months respectively). Females survived longer than males (median 11 months VS 10 months). White and races other than Black survived for a median of 10 months, while Black survived for a median of 9 months higher in other races (21 months). Other details are provided in Table 3.

3.3.2. Univariate analysis of patients who did not receive chemotherapy
Generally, the median overall survival was also noticeably lower in patients who did not receive chemotherapy than those who received it.

Table 2
Univariate and multivariate analyses according to surgery performance comparison.

| Variables                  | Univariate | P-value | Multivariate | Regression coefficient | Univariate | P-value | Multivariate | Regression coefficient |
|----------------------------|------------|---------|--------------|------------------------|------------|---------|--------------|------------------------|
| Age <50 years              |            |         |              |                        |            | <0.001  |              |                        |
| Age ≥50 years              |            |         |              |                        |            |         |              |                        |
| Sex Male                   |            |         |              |                        |            |         |              |                        |
| Female                     | 0.043      |         | 1.143        | (1.074–1.217)          |            |         | 3 (2.92–3.08) | 0.019                  |
| Race White                 |            |         |              |                        |            |         |              |                        |
| Black                      | 0.002      |         | 0.94 (0.897–0.985) | –0.062                |            |         | 3 (2.83–3.166) | 0.952                  |
| Others                     |            |         |              |                        |            |         |              |                        |
| Married                    |            | <0.001  |              |                        |            | <0.001  |              |                        |
| Stage Localized            |            |         |              |                        |            |         |              |                        |
| Regional                   | <0.001     |         |              |                        |            | <0.001  |              |                        |
| Distant                    |            |         |              |                        |            |         |              |                        |
| Grade I                    |            | <0.001  |              |                        |            | <0.001  |              |                        |
| Grade II                   |            |         |              |                        |            |         |              |                        |
| Grade III                  |            |         |              |                        |            |         |              |                        |

* P < 0.05.

b P < 0.001.
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Other details are provided in Table 3.

3.3.5. Multivariate analysis of patients who received chemotherapy

The mortality risk was significantly lower in females than in males (HR, 0.948; 95% CI, 0.914–0.983), while significantly higher in widowed patients (HR, 1.143; 95% CI, 1.081–1.208) compared to married patients. Other details are provided in Table 3.

3.3.4. Multivariate analysis of patients who did not receive chemotherapy

The death risk was significantly higher in patients aged ≥50 years (HR, 1.119; 95% CI, 1.081–1.159), compared to patients <50 years, but significantly lower in females compared to males (HR, 0.917; 95% CI, 0.895–0.941). The death risk was significantly higher in Black (HR, 0.887; 95% CI, 0.864–0.911) compared to White races. The localized stage had a lower risk (HR, 0.941), compared to married patients. Other details are provided in Table 3.

3.4. Univariate and multivariate analyses according to radiation comparison (Table 4)

3.4.1. Univariate analysis of patients who received beam

Patients with ≥50 years survived longer than patients <50 years (median 6 months and 4 months respectively), also females survived longer than males (median 6 months and 5 months respectively). White races lived for a median of 6 months, while Black and other races survived for a median of 5 months. Other details are provided in Table 4.

3.4.2. Univariate analysis of patients who received others

Females survived longer than males (median 5 months and 4 months respectively). Races other than Black and White had a longer survival (median 5 months) than White (median 4 months) and Black races (median 3 months). Other details are provided in Table 4.

3.4.3. Univariate analysis of patients who did not receive radiation

Males and females had the same median survival (10 months). White races lived longer than Black (median 10 and 9 months respectively). However, other races had the longest median survival (12 months). Single patients had the longest median survival (11 months), and separated patients had the least (7 months). The localized stage had a median survival of 13 months, while the distant had a survival of 8 months. Lastly, grade I lived for a median of 10 months, while grade IV lived for a median of 2 months.

3.4.4. Multivariate analysis of patients who received beam

The mortality risk was significantly higher in Black races than White (HR, 1.195; 95% CI, 1.061–1.347) and significantly higher in widowed patients (HR, 1.181; 95% CI, 1.019–1.369) compared to married
Table 4
Univariate and multivariate analyses according to radiation comparison.

| Variables | Beam | Univariate | P-value | Multivariate | Regession coefficient | Others | Univariate | P-value | Multivariate | Regession coefficient | No | Univariate | P-value | Multivariate | Regession coefficient |
|-----------|------|------------|---------|--------------|-----------------------|--------|------------|---------|--------------|-----------------------|----|------------|---------|--------------|-----------------------|
| Age       |      |            | 0.011   |              |                       |        |            | 0.773   |              |                       |    |            | 0.925   |              |                       |
| <50 years | 4    | (3.275–4.725) | Reference | 4 (3.718–4.822) | Reference | 9 (6.58–11.42) | Reference | 10     | (9.428–10.572) |                       |    |            | 1.108   | (1.077–1.141) |                       |
| ≥50 years | 6    | (5.651–6.349) | 0.983   | (0.867–1.114) | −0.017    | 4 (3.899–4.102) | 0.911   | (0.726–1.143) | −0.093               | 10 | (9.403–10.597) | Reference |                       |                       |
| Sex       |      |            | 0.009   |              |                       |        |            | 0.066   |              |                       |    |            | 0.983   |              |                       |
| Male      | 5    | (4.654–5.346) | Reference | 4 (3.899–4.101) | Reference | 10     | Reference | 10     | Reference |                       |    |            | 0.924   | −0.079       |                       |
| Female    | 6    | (5.099–6.901) | 0.972   | (0.874–1.082) | −0.028    | 5 (4.769–5.231) | 0.903   | (0.785–1.039) | −0.102               | 10 | (8.508–11.492) | (0.904–0.944) |                       |                       |
| Race      |      |            | <0.001  |              |                       |        |            | 0.024   |              |                       |    |            | 0.178   |              |                       |
| White     | 6    | (5.545–6.455) | Reference | 4 (3.88–4.12) | Reference | 10     | Reference | 10     | Reference |                       |    |            | 1.059   | 0.058        |                       |
| Black     | 5    | (4.318–5.682) | 1.195   | (1.06–1.347) | 0.178     | 3 (2.797–3.203) | 1.121   | (0.956–1.314) | 0.114                 | 10 | (9.326–10.674) | (1.033–1.086) |                       |                       |
| Others    | 5    | (4.375–5.625) | 1.103   | (0.99–1.229) | 0.098     | 5 (4.753–5.247) | 0.823   | (0.703–0.963) | −0.195               | 12 | (10.132–13.868) | (0.859–0.898) |                       |                       |
| Marital   |      |            | 0.503   |              |                       |        |            | 0.189   |              |                       |    |            | <0.001  |              |                       |
| status    | Married | 5    | (4.595–5.405) | Reference | 5 (4.851–5.149) | Reference | 10     | Reference | 10     | Reference |                       |    |            | 0.912   |              |                       |
| Single    | 5    | (4.347–5.653) | 1 (0.897–1.116) | 0        | 4 (3.8–4.2) | 0.959 | (0.824–1.116) | −0.042 |                       |                       |    |            | 1.121   | 0.114        |                       |
| Separated | 6    | (4.312–7.688) | 1.06    | (0.763–1.471) | 0.058     | 5 (4.117–5.883) | 1.32    | (0.852–2.046) | 0.278                 | 11 | (9.382–12.618) | (1.095–1.146) |                       |                       |
| Divorced  | 6    | (4.869–7.131) | 0.988   | (0.872–1.12)  | −0.012    | 5 (4.7–5.3)  | 1.059   | (0.896–1.252) | 0.058                 | 10 | (8.872–11.128) | (1.044–1.102) |                       |                       |
| Widowed   | 5    | (3.827–6.173) | 1.181   | (1.019–1.369) | 0.166     | 3 (2.809–3.191) | 0.989   | (0.803–1.219) | −0.011               | 10 | (7.912–12.909) | (1.274–1.351) |                       |                       |
| Stage     |      |            | <0.001  |              |                       |        |            | <0.001  |              |                       |    |            | 13      |              |                       |
| Localized | 14   | (12.683–15.317) | Reference | 9 (8.722–9.728) | Reference | 13     | Reference | 13     | Reference |                       |    |            | (11.902–14.098) |                       |                       |
| Regional  | 7    | (5.862–8.138) | 1.439   | (1.261–1.643) | 0.364     | 3 (2.883–3.117) | 1.388   | (1.235–1.561) | 0.328                 | 9  | (8.366–9.634) | (1.551–1.613) |                       |                       |
| Distant   | 4    | (3.728–4.272) | 2.287   | (2.046–2.557) | 0.827     | 1 (0.939–1.061) | 1.786   | (1.48–2.156)  | 0.58                  | 8  | (6.606–9.394) | (2.511–2.637) |                       |                       |
| Grade     |      |            | <0.001  |              |                       |        |            | 0.016   |              |                       |    |            | 10      |              |                       |
| I         | 9    | (7.166–10.834) | Reference | 12     | (9.827–14.173) | Reference | 10     | Reference | 10     | Reference |                       |    |            | (9.435–10.565) |                       |                       |
| II        | 7    | (5.897–8.103) | 1.129   | (0.946–1.349) | 0.122     | 12 (10.463–13.537) | 1.102   | (0.89–1.366) | 0.998                 | 8  | (7.559–8.441) | (0.961–1.031) |                       |                       |
| III       | 4    | (3.26–4.74) | 1.594   | (1.335–1.903) | 0.466     | 8 (6.643–9.357) | 1.71    | (1.321–2.214) | 0.536                 | 3  | (2.807–3.193) | 1.696   | (1.631–1.764) |                       |                       |
| IV        | 4    | (1.456–6.544) | 1.694   | (1.138–2.524) | 0.527     | 9 (4.999–13.001) | 1.879   | (0.831–4.251) | 0.631                 | 2  | (1.565–2.435) | (1.737–2.076) |                       |                       |

*a* P < 0.05.  
*b* P < 0.001.
patients. Other details are provided in Table 4.

3.5.4. Multivariate analysis of patients who received others

The death risk was significantly lower in patients aged ≥50 years (HR, 0.911; 95% CI, 0.726–1.143) than patients <50 years. The mortality risk was significantly lower in races other than black (HR, 0.823; 95% CI, 0.703–0.963) compared to White races. Other details are provided in Table 4.

3.4.6. Multivariate analysis of patients did not receive radiation

The death risk was significantly higher in patients aged ≥50 years (HR, 1.108; 95% CI, 1.077–1.141), compared to patients <50 years, but significantly lower in females than males (HR, 0.924; 95% CI, 0.904–0.944). The mortality risk was significantly higher in Black, but lower in races other than Black (HR, 1.059; 95% CI, 1.033–1.086) and (HR, 0.879; 95% CI, 0.859–0.898) respectively, compared to White races. Also, the death risk was significantly higher in single, divorced, and widowed patients compared to married ones (HR, 1.121; 95% CI, 1.095–1.146), (HR, 1.072; 95% CI, 1.044–1.102) and (HR, 1.312; 95% CI, 1.274–1.351) respectively. Other details are provided in Table 4.

3.5. Univariate and multivariate analyses according to radiation sequence with surgery comparison (Table 5)

3.5.1. Univariate analysis of patients who received radiation after surgery

Patients with localized stage survived longer than other stages (median 20 months). Also, grade I patients survived longer than other grades (median 18 months).

3.5.2. Univariate analysis of patients who received radiation prior to surgery

Patients aged ≥50 years survived longer than those <50 years (Median 15 and 6 months respectively), and patients with localized stage survived longer than other stages (median 22 months).

3.5.3. Multivariate analysis of patients who received radiation after surgery

The death risk was significantly higher in patients with distant stage compared to the localized one (HR, 2.446; 95% CI, 1.851–3.232). Moreover, the risk was significantly higher in grades III and IV compared with grade I (HR, 2.076; 95% CI, 1.336–3.227) and (HR, 2.48; 95% CI, 1.097–5.608) respectively. Other variables showed no significant results.

3.5.4. Multivariate analysis of patients who received radiation prior to surgery

The death risk was significantly higher in divorced compared with married patients (HR, 2.507; 95% CI, 1.158–5.428). Also, patients having a distant stage compared with the localized one (HR, 4.415; 95% CI, 2.394–8.143). Other variables had no significant results.

### Table 5

Univariate and multivariate analyses according to radiation sequence with surgery comparison.

| Variables | After surgery | Univariate P-value | Multivariate Regression coefficient | Prior to surgery | Univariate P-value | Multivariate Regression coefficient |
|-----------|--------------|-------------------|-------------------------------------|------------------|-------------------|-------------------------------------|
| Age       |              |                   |                                     |                  |                   |                                     |
| <50 years | 9 (5.538–12.462) | 0.249             | Reference                           |                  |                   |                                     |
| ≥50 years | 12 (10.21–13.79)  | 0.125             | 1.05 (0.763–1.445)                   | 0.049            |                   |                                     |
| Sex       |              |                   |                                     |                  |                   |                                     |
| Male      | 11 (9.314–12.686) | 0.955             | Reference                           |                  |                   |                                     |
| Female    | 15 (10.56–19.44)  | 0.898             | 0.916 (0.688–1.219)                  | –0.088           |                   |                                     |
| Race      |              |                   |                                     |                  |                   |                                     |
| White     | 12 (9.972–14.028) | 0.875             | Reference                           |                  |                   |                                     |
| Black     | 11 (5.632–16.368) | 0.924             | 1.265 (0.839–1.909)                  | –0.235           |                   |                                     |
| Others    | 8 (6.28–9.72) | 0.526             | 1.361 (0.992–1.867)                  | 0.308            |                   |                                     |
| Marital status | | | | | | |
| Married   | 19 (9.603–14.397) | 0.023             | Reference                           |                  |                   |                                     |
| Single    | 10 (6.614–13.386) | 0.079             | 1.082 (0.799–1.464)                  | 0.097            |                   |                                     |
| Separated | 4 (0.4178) | 0.726             | 2.066 (0.722–5.916)                  | 0.235            |                   |                                     |
| Divorced  | 14 (4.938–23.062) | 0.115             | 0.985 (0.669–1.406)                  | –0.016           |                   |                                     |
| Widowed   | 8 (0.2127) | 0.258             | 1.294 (0.77–2.176)                   | 0.258            |                   |                                     |
| Stage     |              |                   |                                     |                  |                   |                                     |
| Localized | 20 (17.738–22.262) | 0.001             | Reference                           |                  |                   |                                     |
| Regional  | 15 (11.168–18.832) | 0.115             | 1.122 (0.812–1.551)                  | 0.115            |                   |                                     |
| Distant   | 6 (4.914–7.086) | 0.115             | 2.446 (1.851–3.232)β                 | 0.894            |                   |                                     |
| Grade     |              |                   |                                     |                  |                   |                                     |
| I         | 18 (10.944–25.056) | 0.028             | Reference                           |                  |                   |                                     |
| II        | 15 (10.715–19.285) | 0.115             | 1.167 (0.773–1.761)                  | 0.154            |                   |                                     |
| III       | 9 (6.814–11.186) | 0.763             | 2.076 (1.336–3.227)β                 | 0.731            |                   |                                     |
| IV        | 10 (7.434–12.566) | 0.908             | 2.48 (1.097–5.608)β                 | 0.082            |                   |                                     |

*a* P < 0.05.  
*b* P < 0.001.
4. Discussion

The study showed that for patients aging ≥50 years, there was a higher mortality risk in those who performed surgery, did not receive chemotherapy, or did not receive radiation. However, they had a significantly lower mortality risk in cases receiving other radiation than the beam. Females had lower mortality risk in patients who performed surgery or not, received chemotherapy or not, or did not receive radiation. Patients with localized stage, or grade I had significantly lower mortality risks compared to their respective variable, whether they received any of our studied treatment options or not. Likely, married patients and other races also had a lower mortality risk than other marital statuses and White races. On the other hand, Blacks had a higher mortality risk than Whites.

In older people, choosing palliative treatment options could be due to co-existing medical morbidities. However, Shin et al. showed similar postoperative complications and overall survival in elderly and young patients (N = 233). They concluded that age alone should not be a determining HCC risk factor [14]. Another study also stated that elderly patients, with caution selection, had benefited from the major hepatectomy for large HCC as much as younger ones [15].

Black races had a higher mortality risk compared to White races. Generally, according to the racial/ethnic group, Black patients with HCC have the lowest overall survival [16,17]. This is not fully understood; however, it is probably multifactorial and may include socioeconomic factors and healthcare access variances [18,19]. Shaltiel et al. showed that at HCC diagnosis, in Black patients with a history of HCV infection, the liver fibrosis was significantly less advanced; however, their tumors were more advanced in stage and had worse pathologic prognostic features compared to non-Black patients [20]. Regarding the stages, similar to our results, several studies previously reported lower survival rates in regional and distant stages compared to the localized stage [21, 22].

Similar to our results, a previous SEER study also showed an association between females and better survival in HCC patients, especially in younger cohorts. It is suggested that estrogen might protect against hepatocarcinogenesis and encourage more fortunate biology once HCC develops [23]. Contrary to this, Wu et al. did not report a survival difference between males and females [24].

Our study favored married patients. This could be explained by that, worldwide, being in a committed relationship is associated with a better lifestyle, including decreased smoking and alcohol ingestion, healthier diet, more physical activity, and maintenance of healthy body weight [25–28]. Moreover, marriage can provide social support to relieve some stress and encourage keeping healthy lifestyle habits [29].

There is no enough data about the effect of radiation sequence with surgery in HCC, and this study mainly showed non-significant results. However, Wehling et al. recently stated that patients undergoing liver resection as an initial treatment had a median overall survival of 11.1 years, then those who underwent locoregional ablative intervention had 8.4 years. Initial transarterial chemoembolization treatment modality had 6.3 years median survival, whereas those treated with radiation had 2.9 or 5.5 years only [30].

We recommend future research to investigate other important variables and risk factors as well, such as hepatitis and obesity. We also encourage further investigation of the treatment sequence.

The strengths of this study include that the data are generalizable due to their high quality and precision, as they depend on the data registered in the SEER database. Moreover, the study had a large sample of HCC patients. We analyzed different variables with different treatment options. On the other hand, limitations of this study include the retrospective design and the missing of some important variables such as the environmental and genetic ones.

To conclude, in HCC patients who underwent surgery, those aged ≥50 years and grade II had higher mortality risks. Moreover, widowed, regional and distant stages, and grades III and IV had higher mortality risks whether with surgery, or chemotherapy, or radiation. Females had lower mortality risk in patients who performed surgery or not, received chemotherapy or not, or did not receive radiation. More investigations are needed to assess the radiation sequence with surgery.

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Registration of research studies

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102782.

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