RESEARCH ARTICLE

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Gastric Cancer Survival and Its Predictors in Nepal

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Abstract

Background: In Nepal, gastric cancer was the second most common cause of cancer deaths in males and the fifth most common cause of cancer deaths in females in 2020. Although gastric cancer is a significant public health problem, there have been no studies undertaken in Nepal to determine the survival and predictors of gastric cancer survival. **Methods:** A retrospective cohort study of gastric cancer patients at Bhaktapur Cancer Hospital in Kathmandu Valley, Nepal. Data were analysed from 817 new gastric cancer cases, diagnosed between January 2010 and December 2021. Survival rate was analyzed using Kaplan-Meyer methods, and predictors of gastric cancer survival were analyzed using Cox Regression methods. **Results:** The median overall survival for gastric cancer patients was 19 months since diagnosis. The five-year survival rate was 12%. The predictors for survival were younger age, tumors located in the non-cardia, early stage, treatment by surgery, and treatment by chemotherapy. However, sex, histologic type, tumor grade, tumor subtype, and extent of cancer were not associated with survival. **Conclusion:** In Nepal, the overall survival of patients with gastric cancer was 12%, which is much lower than in high-income countries. Predictors of survival were patient age at diagnosis, the stage at diagnosis, the location of the tumor, and the treatment undertaken, both in Nepal and in high-income countries.

Keywords: Gastric cancer survival- Nepal

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Introduction

Gastric cancer is the fourth leading cause of cancer death worldwide, with 660,175 deaths in 2022 [1]. Gastric cancer is the fifth most diagnosed cancer, with 968,784 gastric cancer cases diagnosed in 2022 [1]. In high human development index (HDI) countries there is a predicted 45% increase in incidence by 2040. However, a disproportionate increase in the incidence, number of deaths and burden of disease is estimated for countries with a low or medium human development index (LHDI or MHDI), predicted increase in incidence to 80% by 2040 [1]. The overall five-year survival for high-income countries (HICs) is 20% to 30% [2]. In Nepal, cancer is a major public health issue with estimated new cancer cases totaling 20,508 in 2020 (8,943 men and 11,565 women) [2]. In 2020, gastric cancer accounted for 10.2% of all cancer deaths in Nepal [2].

Predictors for gastric cancer survival are well documented for HICs, stage at diagnosis, tumor location, patients age, treatment [3]. However, accurate estimation overall survival and predictors for gastric cancer survival for low and middle-income countries (LMICs) is hindered in by a lack of population-based cancer registries [4-7].

For Nepal original research information on overall survival and predictors of gastric cancer survival has not been published, and estimates of gastric cancer incidence relies on neighboring countries [6, 2]. Based on these estimates, gastric cancer has the second highest age-standardized incidence in men (9.0 per 100,000) [2, 8] and the sixth highest age-standardized incidence in women (per 100,000) [6, 2, 8]. The aim of this study was to determine the overall survival and predictors of gastric cancer survival in Nepal.

Materials and Methods

This retrospective cohort study determined the overall survival and predictors of gastric cancer survival. Bhaktapur Cancer Hospital (BCH) is the oldest national cancer specific hospital, in Nepal, located in Kathmandu Valley [9, 6]. Adults (18 years of age or older) who met the eligibility criteria and were diagnosed with gastric cancer between 1st January 2010 and 31st December 2021 were included. This study included all cases of gastric adenocarcinoma (tubular adenocarcinomas, papillary adenocarcinomas, mucinous adenocarcinomas, signet-ring cell carcinomas, and poorly cohesive carcinomas) confirmed histologically using the World Health Organization classification of International Classification

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of Disease for Oncology – 10 [10]. Patients with missing information on age, sex, residential address, date of diagnosis, method of diagnosis, or unknown histological findings were excluded. Patients were also excluded if the patient of their next-of-kin declined to report status to the data collectors.

Sample size

This study assumed minimum hazard ratio to be detected as 1.5 or smaller, the initial power calculation (0.80) determined that a sample size of 191 gastric cancer deaths was required to undertake a survival analysis. Over a 10-year period, there were 951 cases of gastric cancer recorded at Bhaktapur Cancer Hospital. Following application of exclusion criteria, 817 participants were eligible for inclusions. Survival time calculation was based on the date of diagnosis and date of loss to follow-up, death or date of contact. This sample size was calculated using statistical software STATA.

Each patient diagnosed at BCH receives an individual Cancer Identity number (CID) used to link the contact information for next-of-kin [9]. Date of death recorded in the patient medical record was used, or, where no date of death was recorded in the medical records, the patients or their next-of- kin was contacted by telephone to determine vital status. The day, month and year of death and the vital status at the last known follow-up was recorded for each participant. For this study mortality of gastric cancer was the dependent variable and the independent variables were: sex; age; histologic type; extent of cancer; tumor location, grade, size, and stage; as well as treatment type (surgery and no-surgery, chemotherapy and non-chemotherapy, radiotherapy chemotherapy and non-radiotherapy chemotherapy).

Patients' demographic information (sex, age), clinical information (tumor location, histologic type, tumor grade, tumor size, extent of cancer, tumor stage and treatment) and dates of: diagnosis; loss to follow-up; death; or date of contact were recorded by trained data collectors. Data collectors telephoned each patient a maximum of three times and if the patients did not answer the phone, the data collector contacted their next-of-kin to inquire about the survival status. Patients were lost to follow-up when the phone number was unavailable or if no response was obtained after three contact attempts with their next-of-kin. For patients who were lost to follow-up, the date of lost to follow-up based on their last presentation at BCH was obtained from the patient medical record. The vital status of each patient was assessed from 1st January 2022 to 15th February 2022 and recorded as dead, alive or lost to follow-up. The flowchart of the data collection procedure is presented in Figure 1.

Statistical analysis

Demographic, clinical and pathological predictors of survival are described using frequencies and percentages. The survival rate and median survival was estimated using the Kaplan-Meier method. The stage at diagnosis was adjusted to determine the survival by treatment including surgery, chemotherapy and radiotherapy chemotherapy. Differences in the survival rate were calculated by different characteristics, using the log-rank test, and, where crude differences were deemed statistically significant, the variable was then included in the multivariable analysis. Variables that met threshold in univariable models using log-rank tests (p-value < 0.25) as covariates to fit the multivariable Cox regression model; variables showing statistical significance (determined at $p < 0.05$) in multivariable Cox regression analysis were considered as significant predictors associated with survival of gastric cancer patients. Survival was analyzed through a multivariable model that followed a backwards-stepwise approach and included only significant predictors. This efficient analysis limited the number of predictors and reduce the risk of overfitting by removing the least important variables early in the model and leaving the most important variables to determine predictors of survival. All analysis was conducted using the Statistical Analyses Software, Stata version 17.

Results

Demographic, clinical and pathological predictors of survival are described using frequencies and percentages. There were 817 gastric cancer patients diagnosed at BCH between 1st January 2010 and 31st December 2021. Male patients were higher (63.6%) compared to female (36.4%).

Table 1.Demographic Data and Signs and Symptoms for Gastric Cancer Patients Diagnosed between 1st January 2010 and 31st December 2021 at BCH, Nepal.

Variables	Frequency	Percent (%)
Sex		
Male	520	63.6
Female	297	36.4
Age		
18 to < 50	179	22.0
50 to < 65	377	46.5
≥ 65	261	31.5
Residential Province		
Province No. 1	142	17.4
Madhesh Pradesh	74	9.0
Bagmati Pradesh	443	54.3
Gandaki Pradesh	83	10.2
Lumbini Pradesh	35	4.2
Karnali Pradesh	22	2.7
Sudurpashchim Pradesh	18	2.2
Signs and Symptoms		
Abdominal pain	787	95.9
Anorexia	687	84.0
Nausea	618	76.0
Fatigue	602	73.7
Weight loss	537	65.7
Heartburn	366	44.8
Black-coloured faeces	312	38.3
Vomiting	292	35.8
Anaemia	257	31.6

Abdominal pain was the most common presenting signs or symptoms followed by anorexia, nausea and fatigue (Table 1).

Based on a 30-day month, the median overall survival for gastric cancer patients was 19 months since diagnosis. The total person-time of follow-up was 17,808 months. The survival rate was 70% at one year, 37% at two years, 23% at three years, 18% at four years, and 12% at five years (Figure 2).

Male gastric cancer patients had a significantly lower median survival of 17 months since diagnosis (95% CI: 15.7 to 18.4) compared with female patients' survival of 22 months since diagnosis (95% CI: 20.3 to 23.9, P <0.001). These are detailed in Table 2. Survival was dependent on age at diagnosis; a significantly lower median survival of 10 months was determined for those aged greater or equal to 65 years, compared with 30 months for those aged between 18 and 50 years (P <0.001). The extent of the cancer at diagnosis was linked with survival rate; patients with distant gastric cancer metastases had significantly lower median survival (11 months, P < 0.001), compared with localise cancer (71 months, P < 0.001). Staging was associated with survival rate; patients diagnosed with stage IV gastric cancer had ntly lower median survival, of 13 months, compared with stage I and II, of 67 months (P < 0.001). Treatment was also related to survival rate; patients who did not receive any surgery had significantly lower median survival, 9 months, compared with patients who had partial radical gastrectomy, 30 months (P < 0.001). Bypass surgery and palliative gastrectomy had significantly lower median survival of 10 and 15 months respectively, compared with partial-radical gastrectomy of 30 months and total gastrectomy of 30 months (P < 0.001). Patients who did not receive treatment by chemotherapy had significantly lower median survival of 7 months, compared with patients who did receive chemotherapy of 21 months (P < 0.001). Patients who did not receive radiotherapy had significantly lower median survival of 17 months, compared with those who did receive radiotherapy of 26 months (P < 0.005).

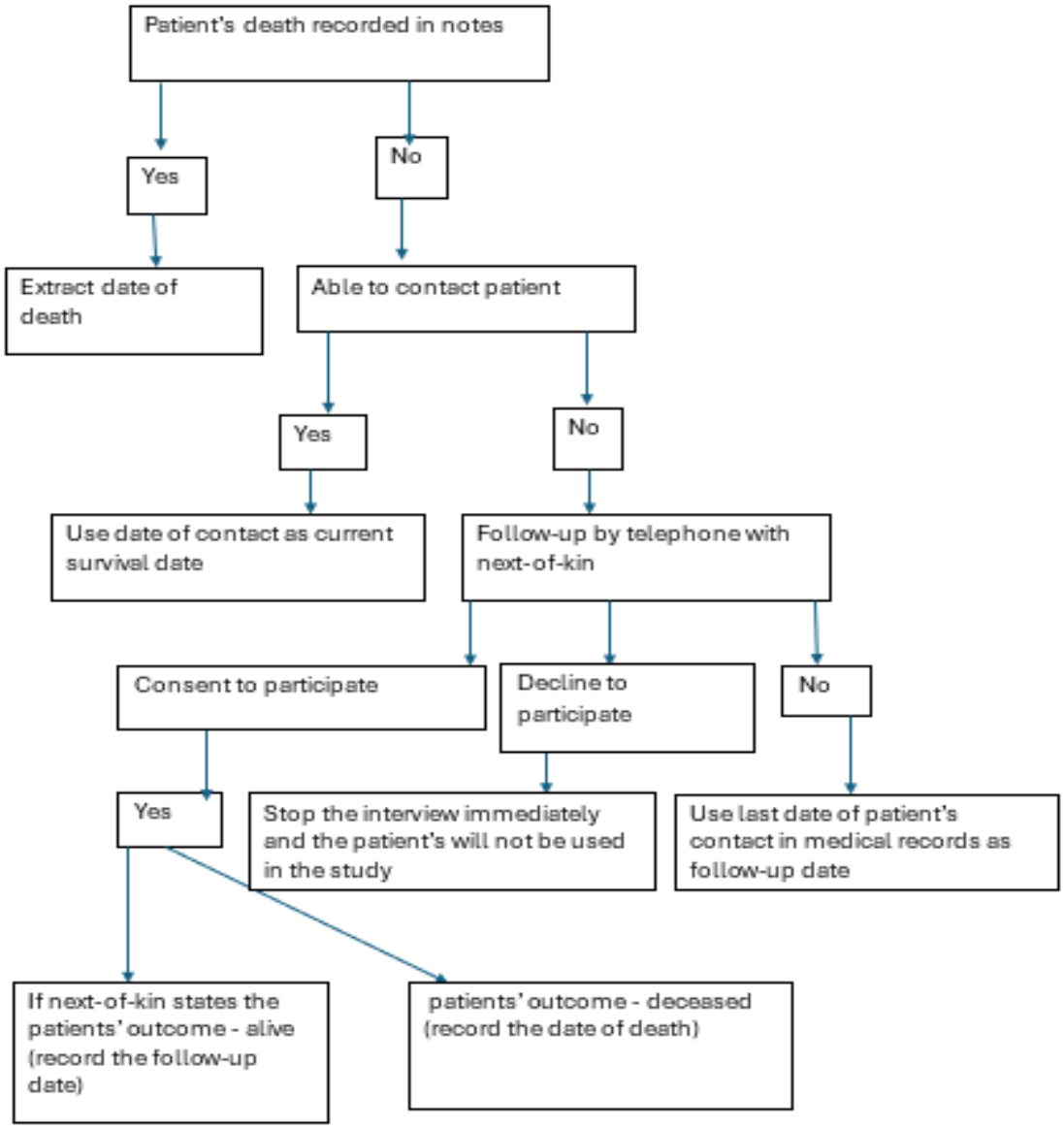

Figure 1. Flowchart for the Data Collection Procedure

Table 2. Covariates and Median Survival Time Since Diagnosis (Months) of Gastric Cancer Patients Diagnosed between 1st January 2010 and 31st December 2021 at BCH, Nepal.

Variables	Median survival time (months)	95% CI	p value (Log-rank)
Sex			0.001
Male	17	15.7 to 18.4	
Female	22	20.3 to 23.9	
Age (years)			<0.001
18 to <50	30	26.3 to 33.6	
50 to <65	21	19.3 to 22.6	
≥ 65	10	9.1 to 10.8	
Tumor location			0.25
Distal cancer	19	17.4 to 20.5	
Proximal cancer	18	13.9 to 22.1	
Histologic type			0.79
Tubular adenocarcinoma	18	15.9 to 20.0	
Mucinous adenocarcinoma	20	16.6 to 23.3	
Papillary adenocarcinoma	23	10.7 to 35.2	
Poorly-cohesive carcinoma	19	12.9 to 25.0	
Signet-ring-cell carcinoma	18	15.5 to 20.4	
Tumor grade			0.44
Well-differentiated	21	16.2 to 25.8	
Moderately-differentiated	19	16.9 to 21.1	
Poorly-differentiated	17	14.9 to 19.1	
Un-differentiated	17	13.4 to 20.5	
Tumor size			0.85
<3 cm	18	14.2 to 21.7	
3 to 6 com	18	15.5 to 20.4	
>6 cm	19	16.9 to 21.1	
Extent of cancer			<0.001
Localised	71	55.9 to 86.1	
Regional	63	52.9 to 73.1	
Locally advanced	22	20.6 to 23.9	
Distant metastases	11	10.0 to 12.1	
Tumor stage			<0.001
Stage I and II	67	59.1 to 74.8	
Stage III	22	20.5 to 23.4	
Stage IV	13	11.5 to 14.4	
Treatment-by surgery			<0.001
Partial-radical gastrectomy	30	26.9 to 33.1	
Total-radical gastrectomy	30	22.9 to 37.0	
Bypass surgery	10	8.5 to 11.4	
Palliative gastrectomy	15	13.8 to 16.1	
No surgery	9	8.1 to 9.8	
Treatment by chemotherapy			<0.001
Yes	21	19.3 to 22.6	
No	7	5.9 to 8.1	
Treatment by radiotherapy chemotherapy			0.005
Yes	26	22.5 to 29.4	
No	17	15.5 to 18.4	

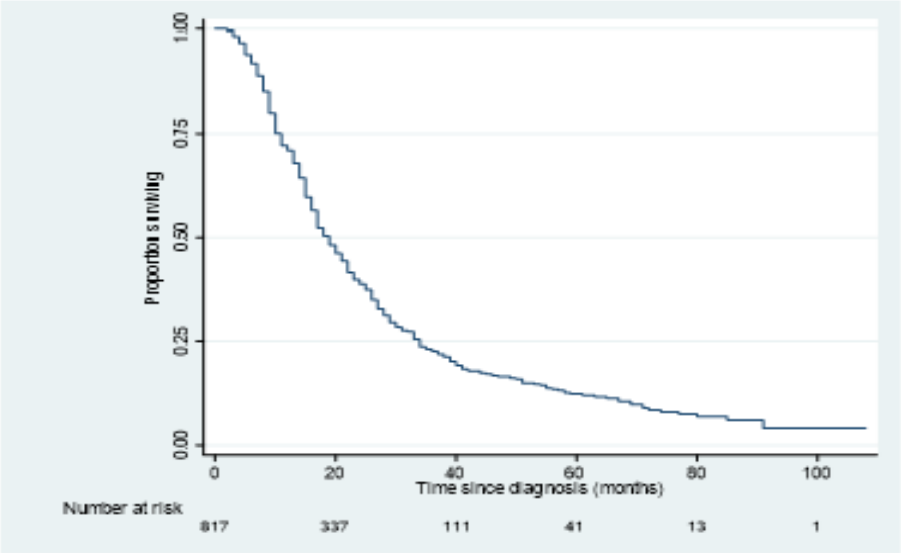

Figure 2. Overall Survival Rate of Patients with Gastric Cancer Diagnosed at BCH between 1 January 2010 and 31 December 2021.

There was a higher risk of death for patients in stage III (HR: 6.81; 95% CI: 4.9 to 9.3, P < 0.001) and stage IV (HR: 8.27; 95% CI: 5.7 to 12.2, P < 0.001) compared to patients in stage I and II. These are detailed in Table 3. There was a higher risk of death for patients in the non-surgical treatment group (HR: 2.94; 95% CI: 2.7 to 4.2, P < 0.001) compared with partial radical gastrectomy. A higher risk of death was observed in palliative gastrectomy (HR: 2.03; 95% CI: 1.4 to 2.9, P < 0.001) and bypass surgery (HR: 2.84; 95% CI: 1.9 to 4.1, P < 0.001) compared to partial radical gastrectomy. The risk of death by total radical gastrectomy (HR: 0.81; 95% CI: 0.5 to 1.2, P < 0.001) was lower compared with partial radical gastrectomy. There was a higher risk of death for patients to treatment by non-chemotherapy group compared to treatment by chemotherapy (HR: 2.51; 95% CI: 1.8 to 3.4, P < 0.001).

Discussion

This study determined the overall survival and predictors of gastric cancer patients diagnosed at BCH Nepal. Significant covariates were age at diagnosis, tumor location, tumor stage at diagnosis, treatment by surgery, and treatment by chemotherapy. The overall 5-year survival rate, of 12%, was significantly lower than overall survival rate in high income countries (HIC) of 20 to 29% in Kuwait, Turkey, Finland, France; 30 to 40% in Canada,

Table 3. Multivariable Analysis of Factors Associated with Mortality of Gastric Cancer Diagnosed at BCH

Variable	Hazard ratio (HR)	95% CI	P value
Age	1.15	1.1 to 1.2	<0.001
Tumor location			0.02
Distal cancer	Reference		
Proximal cancer	1.44	1.1 to 2.9	
Tumor stage			<0.001
Stage I and II	Reference		
Stage III	6.81	4.9 to 9.3	
Stage IV	8.27	5.7 to 12.2	
Treatment by surgery			<0.001
Partial radical gastrectomy	Reference		
Total radical gastrectomy	0.81	0.5 to 1.2	
Bypass surgery	2.84	1.9 to 4.1	
Palliative gastrectomy	2.03	1.4 to 2.9	
No surgery	2.94	2.7 to 4.2	
Treatment by chemotherapy			<0.001
Yes	Reference		
No	2.51	1.8 to 3.4	

Note: Variable that were adjusted for – sex, age, tumor location, extent of cancer, tumor stage, treatment by surgery, treatment by chemotherapy, and treatment by radiotherapy chemotherapy.

USA, Malaysia, Italy, Belgium, Switzerland; and 60 to 70% in Korea and Japan [11, 12]. The exception was in India, a culturally similar neighboring country to Nepal, with a 8.9% overall survival rate in India [11]. In this study the median age at diagnosis was 60 years, compared to 70 to 75 years in HICs including Australia, Canada, Denmark, United Kingdom, New Zealand [11, 12].

In this study, the three-year survival was 88% and 18.7% of patients were classified in stage I and II. This high percentage of patients diagnosed in the early stage may be due to combining the staging of I and II, causing skewness and reducing effectiveness of the analysis model. The early diagnosis three year survival was much lower in Canadian study, at 62% for Stage I and 50% for stage II [8]) and in Ireland, stage I was 85%, and stage II 58% [8].In this study the three-year survival was 45.9% of patients were classified at stage III, lower in this study compared to 20% survival in HICs. In Canada, the three-year survival rate for diagnosis at stage III was 34% [8]. Ireland, the three-year survival was higher for diagnosis at all stages compared to Nepal; stage III was 40% [8]. In Denmark, the three-year survival rate, for diagnosis at stage was III 29.7% [8]. in this study 35.4% of patients were classified at stage IV, however, the three-year survival for diagnosis at stage IV was higher, at 5% compared to both Canada and Denmark, where the three-year survival for diagnosis at stage IV was only 4%. In Ireland, the three-year survival was higher for diagnosis at all stages compared to Nepal; stage IV was 8% [8].

This study demonstrated a lower overall survival in the older age group (≥65 years) diagnosed with stage IV gastric cancer compared to younger age group (18 to <50 years) with 40.4% of the older aged group diagnosed at stage IV compared to 16.0% in younger age group, which contributed to a lower overall survival in Nepal. Previous studies also reported lower survival in older age group diagnosed with stage IV gastric cancer, suggesting that early diagnosis is crucial for improved survival [13, 14, 3].

In this study the majority of patients (83.7%) were diagnosed with distal gastric cancer, and only 16.3% diagnosed with proximal gastric cancer. The five-year survival for proximal gastric cancer is lower (10%) compared to distal gastric cancer (15%), due to the more aggressive behavior of cardia-originating cancer and more likely diagnosed at an advanced stages, compared to distal gastric cancer. Previous studies have confirm lower survival for proximal gastric cancer compared to distal gastric cancer, however, there is a lack of evidence from comparable countries [3, 15].

In this study, patients who underwent partial radical gastrectomy had a higher five-year survival (25%) compared to patients who underwent total radical gastrectomy (15%), while patients who did not undergo surgery had a significantly lower five-year survival (5%). This difference was also found in other studies from HICs - Italy and Japan, patients who underwent partial radical gastrectomy had a higher five-year survival (65.3% and 76.3%) compared to patients who underwent total radical gastrectomy (62.4% and 55.9%) [16, 17]. A study from India demonstrated no survival at five-year for patients who underwent partial radical gastrectomy and total radical gastrectomy [18].

In this study, the five-year survival for patients who received chemotherapy was 15% This was lower than findings from a similar study from Iran that found a 30% five-year survival for patients who received chemotherapy [18]. In this study, the five-year survival was 0% in patients who did not receive chemotherapy and in the Iranian study the five-year survival for patients who did not receive chemotherapy was also 0% [18]. Similar findings were confirmed by studies from HICs, that determined a positive impact of chemotherapy on survival [19, 20].

Strengths and limitations

One of the strengths of this study is the representative sample size as the number of participants was adequate to determine the survival rate of gastric cancer patients, based on power calculation. Another strength is the long-time frame for follow-up of up to 12 years for incident gastric cancer patients between 1st January 2010 and 31st December 2021. A further strength of this study is the wide range of clinical predictors that enable the determination of associations with survival. As this study design was retrospective, the data available was initially collected for treatment purposes, not research purposes, therefore, data collection tools were developed to maximize accuracy of information from existing variables, while retaining study feasibility.

As data were unavailable regarding; socioeconomic status, ethnicity and the specific type of treatment, this study was unable to determine the association between these variables and survival of gastric cancer patients. Additionally, this study was unable to compare survival associated with the type of treatment: chemotherapy (adjuvant vs neo-adjuvant) and radiotherapy (adjuvant vs neo-adjuvant).

A survival bias may have occurred due to delay between diagnosis and commencement of treatment, duration of treatment or cyclical nature of the treatment [21]. Also, there may be some confounding of treatment-status that has been adjusted for the effect of potential confounders, sex, age, tumor location, extent of cancer, tumor stage and treatment. This survival analysis study was limited to the predictors of gastric cancer survival, however evidence on risk factors, causal factors and explanatory factors would provide practical information to inform practice and policy on gastric cancer care.

In conclusions, the overall survival of patients with gastric cancer was lower in Nepal compared with HICs. Factors affecting overall survival were age, tumor locations, tumor stage, treatment by surgery and treatment by chemotherapy. However, survival was not associated with sex, histologic type, tumor grade, tumor subtype and extent of cancer. This study provides the first benchmark for improving gastric cancer care in Nepal. Future studies that include detailed socio-economic information for patients diagnosed with gastric cancer and provider perspectives would improve the quality of care and outcomes in Nepal.

Author Contribution Statement

Krishna Poudel contributed to the design and drafted the initial manuscript. Deborah Sims revised the manuscript and contributed to the final revision. Deependra Singh revised the manuscript and contributed to the final revision.

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Approval

It is part of an approved PhD student thesis.

Ethical declaration

Ethical approval was obtained from University of Technology Sydney, Bhaktapur Cancer Hospital and Nepal Health Research Council.

Data availability

University of Technology Sydney STACH Database.

Funding statement

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Conflict of Interest

The authors declare no conflicts of interest.

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