

# One-year Incidence and Standardized Mortality Rates for Esophageal Squamous Cell Carcinoma in Uganda

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## Research Article

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# Abstract

**Background:** Little is known about the survival of patients with esophageal squamous cell cancer in resource limited settings.

**Objectives:** We sought to determine the incidence of one-year all-cause mortality and age-standardized mortality rates for esophageal squamous cell carcinoma in Uganda.

**Methods:** Prospective cohort of 92 participants with histologically confirmed esophageal squamous cell cancer at Mbarara Regional Referral Hospital, southwestern Uganda. Participants were enrolled between January 2018 and March 2020 and followed until death. We used Kaplan-Meier methods to determine all-cause mortality and median survival time; Cox regression to determine predictors of survival; and determined age-standardized mortality rates (SMR) using the WHO standard population.

**Results:** All 92 participants contributed a total 353.8 months at risk, 89 (96.7%) died representing an incidence rate of 251.5 (95% CI 204.3, 309.6) per 1000 person-months. The difference in the one-year risk of all-cause mortality among men and women was negative 6.4 percentage points. The overall SMR was 9.96 (95%CI 7.63, 12.29) per 100,000 and median survival time was 3.03 (95% CI 2.60, 3.47), shortest (1.77 months) among men younger than 45 and longest (7.77 months) among women aged 75 years or greater. In a fully adjusted model, high socioeconomic status predicted longer survival while increasing age and low socioeconomic status predicted shorter survival.

**Conclusion:** After diagnosis, the one-year incidence rates of all-cause mortality and age-standardized mortality rates among ESCC patients in rural Uganda are high. Initiatives to improve access to oncology care for diagnosis and treatment should be prioritized to improve overall survival.

## Introduction

Esophageal cancer is the eighth most prevalent cancer worldwide.[1–3] In Asia and east and southern Africa, esophageal squamous cell carcinoma (ESCC)— a subtype of esophageal cancer that accounts for at least 90 % of all global esophageal cancers— is common.[2] For example, the International Agency For Research on Cancer (IARC) in 2012 estimated the age-standardized incidence rates of esophageal cancer among Ugandan men as 36.7 per 100,000 and 24.8 per 100,000 among women compared to the worldwide age-standardized incidence rates of 16.5 for men and 8.9 per 100,000 for women.[4]

Despite advances in clinical oncology, the 5-year survival rate for esophageal cancer remains poor, ranging from 15–25% worldwide.[5] Though the 5-year relative survival rate is higher in high income countries [6], survival is much lower (< 10%) in low and middle income countries with less developed medical infrastructure [7] partly due to patients presenting late, with locally advanced disease or metastases, resulting in very poor survival. Advances in novel chemoradiotherapy regimes[8] provide the opportunity to improve patient outcomes when disease is discovered at an early stage.

However, available data on ESCC incidence in African countries are derived from national cancer registries which are sparse covering 11% of the total African populations[9]. These registries often cover small, subnational, and urban areas and are not representative of national populations. Mortality data is often deficient due to insufficient follow-up, therefore the IARC mortality estimates are based on national mortality and survival probabilities[4] which are skewed in low and middle income countries (LMICs) due to incomplete population coverage. These results in implausibly low mortality rates, and poor-quality data on cause of death information. Given the sparsity of cancer registries, hospital-based data with vital status of ESCC patients provides a unique and relatively unbiased source of ESCC mortality incidence. High quality data on ESCC mortality is paramount for appropriate resource allocation by governments/stakeholders for prevention, diagnostics and treatment initiatives.

We aim to determine the ESCC mortality incidence rate, age-standardized mortality rate, and predictors of ESCC survival in Uganda to highlight the need for high quality data on cancer mortality. Without this detailed knowledge, we may have extreme difficulty formulating strategies to reduce ESCC mortality and morbidity.

## **Materials And Methods**

### **Study design**

We conducted a case-only prospective cohort study nested in Polycyclic Aromatic hydrocarbon exposures and Dietary Risk of Esophageal squamous cell carcinoma in southwestern Uganda (PADRE) study a case-control study that enrolled participants between January 2018 and March 2020 in the endoscopy unit of Mbarara Regional Referral Hospital (MRRH), southwestern Uganda previously described.[10]. Briefly, patients with gastrointestinal symptoms are referred from within MRRH and southwestern Uganda for esophagogastrosocopy at MRRH. In this setting, patients for upper gastrointestinal endoscopy often present with advanced ESCC disease (stage III or stage IV). For this study, participants were patients who were diagnosed with ESCC at esophagogastrosocopy and tissue histology. To be eligible for the study, ESCC cases had to be 18 years or greater, never have been diagnosed or treated for ESCC. Patients with no features of esophageal masses on EGD and histology findings other than ESCC were excluded.

After written informed consent, esophagogastrosocopy was performed to characterize abnormalities in the esophagus and collect esophageal tissue for histology. During diagnostic upper gastrointestinal endoscopy, we collected information about any suspicious esophageal lesions, describing the location i.e., upper third (15–24 cm), middle third (24–32 cm), and lower third (32–40 cm), traversibility (accessing if one could pass the scope beyond the lesion – indicating if the lesion was obstructive in nature), and collecting 3 esophageal biopsies for histology.[10] At the MUST histopathology laboratory, esophageal biopsies were processed and stained with Hematoxylin and eosin.

Slides containing the stained histopathological specimens were then examined using standard diagnostic criteria for microscopic atypia for esophageal squamous cell carcinoma, pathologist reported

features such as presence of nuclear atypia, prominent keratinization and evidence of invasion. [11]

Interviews were conducted at the endoscopy unit of Mbarara Regional Referral Hospital (MRRH) to obtain socio-demographic information including age, gender, and socioeconomic status based on ownership of household items. We also extracted clinical data from clinical records including family history of diagnosed gastrointestinal cancer, symptoms at presentation to MRRH and associated durations.

Of note, participants had the discretion to accept/decline chemotherapy and cancer management was at the discretion of the Oncology physicians. The chemotherapeutic regimen used for ESCC at MRRH is *Cisplatin* and *5-fluorouracil (5-FU)*. This is provided free of charge when available otherwise if not available patients' pay out of pocket from private pharmacies. Radiotherapy is only administered at Uganda Cancer Institute (UCI), Kampala.

Each participant was requested to provide a list of at least 3 of their telephone contacts, those of a relative living with participant or neighbor to enable locating the participant. Participants were actively followed every month post-hospital discharge until death.

## Data analysis

We used principal component analysis to generate an assets index score based on household utilities and assets to derive composite measures of socioeconomic status with highest discriminatory capabilities. Participants were divided into tertiles (low, fair, and high socioeconomic status).

Participant demographic and clinical characteristics were summarized for the entire group: means (sd) for continuous variables and counts (percentages) for categorical variables. The follow-up time was the time interval from EGD test to death. Participants who were alive at their last follow-up were censored at the last follow-up date (December 1, 2020).

The primary outcome was overall survival over one year of follow-up. Kaplan-Meier analysis was used for estimating survival probabilities for the overall sample, gender, and socioeconomic status.

Multivariable Cox proportional hazards regression analysis was performed to identify potential factors associated with hazard of death. We adjusted for Age, gender, socioeconomic status, and family history of upper gastrointestinal cancer (Buccal cavity, esophagus, and stomach) (model 1). In model 2, we further adjusted model 1 for measures of disease severity such as untraversability of esophageal lesion during EGD (obstruction), anemia (hemoglobin <7mg/dL), histological features (cell differentiation and invasion of the stromal layer) and in model 3 we adjusted model 2 for receipt of chemoradiotherapy to control the possibility of confounding by indication. We conducted these analyses in a sample with all available data and those with complete data on all covariates.

For comparability of mortality rates across regions and time, we calculated age-standardized mortality rates (SMRs) separately for men and women within the age groups (30 to 45, 45 to 54, 55 to 64, 65 to 74,

and 75 or greater) using direct standardization to the World Health Organization Standard Population age-structure for the period 2000-2025.[12] The overall rates by strata indicate the rate that would result if all populations had the same age distribution.[13]

All analyses were performed using Stata version 15.1 (Stata Corp., TX, USA). We determined statistical significance by a 2-sided p-value of less than 0.05.

## Results

Of the 125 patients screened between January 2018 and March 2020, 92 participants were enrolled after 33 were excluded from the group of potential cases: 14 had esophageal adenocarcinoma presenting as lower esophageal tumors, 12 declined consent, 2 had Barrett's esophagus, 2 died before interviews, 2 were mentally incapacitated, and 1 lived in northwestern Tanzania which would make follow-up challenging.

Participant characteristics are summarized in Table 1. The mean age at diagnosis was 61.3 years (SD 11.3) (range 33 years to 95 years) and the most common presenting complaint was dysphagia to liquids among 79 (88.9%) participants with a median duration of 12 weeks (IQR 8, 20) weeks). Seventy (76.9 %) participants had obstructive lesion untraversable on EGD (circumference of 3.8 mm). Only 10 participants received chemoradiotherapy (equally distributed by socioeconomic status).

Table 1  
Baseline characteristics of participants with ESCC, PADRE study 2020.

Characteristic	N = 92
Men	73 (79.3)
Age	
Mean (SD)	61.3 (11.3)
Range (min, max)	62 (33, 95)
Family history of upper GI cancer	42 (45.7)
Primary symptom	
Dysphagia for liquids	79 (88.9)
Odynophagia	6 (6.5)
Median duration (in weeks) of symptom (median, IQR)	12 (8, 20)
Secondary symptom	
Odynophagia	23 (25.0)
Epigastric pain	20 (21.7)
Regurgitation	16 (17.4)
Median duration (in weeks) of symptom (median, IQR)	12 (8, 24)
Tumor site	
Upper Esophagus (< 24 cm from incisors)	13 (19.1)
Mid Esophagus (24 to 32 cm from incisors)	51 (75.0)
Lower Esophagus (> 32 cm from incisors)	4 (5.9)
Obstruction	70 (76.9)
ICDO Differentiation	
None (Gx)	12 (13.0)
Well (Grade 1)	5 (5.4)
Moderate (Grade 2)	37 (40.2)
Poor (Grade 3)	38 (41.3)
Therapy	

SD: standard deviation; IQR: interquartile range; GI: Gastrointestinal; ICDO: International Classification of Disease for Oncology

Characteristic	N = 92
Palliation	82 (89.1)
Chemoradiotherapy	10 (10.9)
SD: standard deviation; IQR: interquartile range; GI: Gastrointestinal; ICDO: International Classification of Disease for Oncology	

For a total analysis time at risk and under observation of 353.8 months (29.5 years), 89 (96.7 %) participants died representing an incidence rate of 251.5 (95% CI 204.3, 309.6) per 1000 person-months and overall survival of 3.26 % in 1 year. Men contributed a total 265.5 person-months of observation time in which 71 died representing an incident rate of 267.4 (95% CI 211.9, 337.4) per 1000 person-months whereas women contributed 88.34 person-months of observation in which 18 died representing an incident rate of 203.7 (95% CI 128.3, 323.3) per 1000 person-months. Table 2. The difference in the one-year risk of all-cause mortality among Ugandan men and women with ESCC was negative 6.4 percentage points 95%CI (-17.6, 4.9).

Table 2

Median survival time and incidence rates of all-cause mortality of ESCC participants, PADRE study 2020.

Characteristic	Person-months	Deaths	Median survival (in months) (95% CI)	Incidence rate (95% CI) per 1000 person-months
Overall	353.82	89	3.03 (2.60, 3.47)	251.54 (204.35, 309.62)
Gender				
Men	265.48	71	3.00 (2.50, 3.47)	267.44 (211.93, 337.47)
Women	88.34	18	3.17 (2.17, 4.83)	203.75 (128.37, 323.40)
Age (in years)				
30 to 45	26.97	7	3.07 (1.37, 7.10)	259.58 (123.75, 544.50)
45 to 54	66.73	20	2.83 (1.37, 3.90)	299.70 (193.35, 464.54)
55 to 64	113.5	33	3.33 (2.17, 3.87)	290.75 (206.70, 408.97)
65 to 74	53.51	14	2.40 (0.73, 3.47)	261.64 (154.96, 441.77)
75 or greater	93.12	15	3.87 (2.50, 5.97)	161.09 (97.11, 267.20)
Socioeconomic status				
Low	52.13	32	1.50 (1.10, 1.90)	613.81 (434.07, 867.97)
Fair	96.60	30	3.07 (2.83, 3.67)	310.56 (217.14, 444.17)
High	205.09	27	5.77 (4.33, 7.77)	131.65 (90.28, 191.97)
Tumor site				
Upper	116.61	36	2.67 (2.10, 3.00)	308.72 (222.69, 428.00)
Mid	214.32	49	3.40 (2.77, 4.23)	228.63 (172.80, 302.51)
Lower	22.9	4	3.87 (1.77, 5.97)	174.67 (65.56, 465.40)
CI: confidence interval				

The overall median survival time was 3.03 months (95% CI 2.60, 3.47) Fig. 1; 3.00 months (95% CI 2.50, 3.47) among men and 3.17 months (95% CI 2.17, 4.83) among women. Of note, men of age < 45 years had the lowest median survival time of 1.77 months while women aged 75 years or greater had the longest median survival time of 7.77 months. Table 2.

The Kaplan-Meier survival curves for overall survival for the whole population, categorized by gender, and asset index, and therapy are shown in Fig. 1. Of note, median survival was higher among those who



received chemoradiotherapy was at 4.23 months (95%CI 0.63, 9.20) compared those who received palliative care only of 2.97 months (95% CI 2.40, 3.33).

The overall estimated age-standardized mortality rates (SMRs) was 9.96 (95%CI 7.63, 12.29) per 100,000; for men was 10.08 (7.46, 12.69) per 100,000 and 9.64 (4.17, 15.11) per 100,00 for women as shown in Table 3. Within the age groups, the SMRs for both sexes tended to decrease with increasing age. Due to the limited study population, it was feasible to further categorize gender by age groups. Hence, these results do not rule out a general decreasing trend in SMRs across age groups.

Table 3  
Crude and age-standardized# group-specific mortality rates, PADRE study 2020

Characteristic	Crude mortality rate per 100,000	Age standardised# mortality rate (95% CI) per 100,000
Overall	11.54	9.96 (7.63, 12.29)
Gender		
Men	11.57	10.08 (7.46, 12.69)
Women	11.40	9.64 (4.17, 15.11)
Age (in years)		
30 to 45	4.68	2.03 (0.52, 3.53)
45 to 54	8.76	2.03 (1.14, 2.92)
55 to 64	11.72	1.96 (1.28, 2.65)
65 to 74	18.07	1.89 (0.90, 2.88)
75 or greater	32.76	2.03 (1.06, 2.99)
#standardized to the World population (2000 to 2025); CI: Confidence interval		

In the minimally adjusted multivariable Cox proportional hazards regression model 1, predictors of increased hazard of death were age (aHR 1.01, 95% CI 1.01 to 1.01); low socioeconomic status (aHR 4.62, 95% CI 2.50 to 8.54) whereas being in the highest SES group predicted reduced hazard of death (aHR 0.40, 95% CI 0.23 to 0.70). In contrast, for model 2, increasing age (aHR 1.01, 95% CI 1.01 to 1.01), low socioeconomic status (aHR 8.97, 95% CI 3.72 to 21.65), cell differentiation grade 2 (aHR 3.05, 95% CI 1.10 to 8.47) predicted increased hazard of death and high socioeconomic status (aHR 0.46, 95% CI 0.23 to 0.92) predicted lower hazard of death. In the full adjusted model 3, predictors of increased hazard of death included increasing age (aHR 1.01, 95% CI 1.01 to 1.01) and low socioeconomic status (aHR 4.57, 95% CI 2.33 to 8.96) while high SES was associated reduced hazard of death (aHR 0.39, 95% CI 0.21 to 0.70) as seen in Table 4.

Table 4  
Predictors of overall survival following ESCC diagnosis in Uganda, PADRE study 2020

Characteristics (N = 92)	Adjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)
	AIC = 440	AIC = 445	AIC = 446
Age (each year)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Gender			
Men	1.37 (0.79, 2.37)	1.82 (0.84, 3.95)	1.33 (0.71, 2.47)
Women	Ref	Ref	Ref
Socioeconomic status			
Low	4.62 (2.50, 8.54)	8.97 (3.72, 21.65)	4.57 (2.33, 8.96)
Fair			
High	0.40 (0.23, 0.70)	0.46 (0.23, 0.92)	0.39 (0.21, 0.70)
Family history of GI cancer	0.98 (0.65, 1.49)	1.11 (0.62, 1.98)	1.05 (0.65, 1.69)
Traversability of lesions on EGD			
Traversable		Ref	Ref
Obstruct	-	0.90 (0.56, 1.44)	0.83 (0.51, 1.37)
Hemoglobin*			
Normal		Ref	Ref
Low	-	1.80 (0.90, 3.60)	1.49 (0.84, 2.66)
Cell differentiation			
None (Gx)	-	Ref	Ref
Well (G1)	-	1.91 (0.43, 8.43)	0.98 (0.23, 4.15)
Moderate (G2)	-	3.05 (1.10, 8.47)	1.25 (0.50, 3.10)
Poor (G3)	-	1.57 (0.50, 4.90)	0.70 (0.32, 1.52)
Invasion of stroma			
No	-	0.41 (0.19, 0.88)	0.75 (0.44, 1.26)
Yes	-	Ref	Ref

AIC: Akaike's information criterion; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal;  
\*Hemoglobin levels were categorized as normal if > 13.5 mg/dL for men or > 12.0 mg/dL for women

Characteristics (N = 92)	Adjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)
Therapy			
Palliative care only	-	-	Ref
Chemoradiotherapy	-	-	0.42 (0.14, 1.28)
AIC: Akaike's information criterion; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal; *Hemoglobin levels were categorized as normal if > 13.5 mg/dL for men or > 12.0 mg/dL for women			

## Discussion

In this single center prospective cohort study of ESCC participants followed from diagnosis until death, we found a low overall survival of 3.26% in 1 year which translates to a high incidence rate of one-year all-cause mortality and low (3 months) median survival. Unsurprisingly, men had the highest incidence rate of one-year mortality and lowest median survival compared to women. The high incidence of all-cause mortality relates in part to advanced disease at presentation, and disparities in access to treatment as evidenced by the longer overall median survival among those who receive chemoradiotherapy compared to those who did not. However, this overall median survival is shorter in contrast to a 9 months median post treatment survival reported by a meta-analysis of African studies. [14]

Our results corroborate those of an Iranian study which found a very poor (< 19% five-year overall survival rate) and women having a longer survival than men.[15] The influence of gender on survival could be due to differences in ESCC distribution with a male to female ratio of 1:4, and the exposure to ESCC risk factors (as smoking and drinking alcohol) which heavily influence both cancer incidence and competing mortality are likely to be more frequent in men with ESCC; however, further investigation is required to better interpret this interesting result.

Our finding of a median survival of 4.23 months among those who received chemoradiotherapy corroborates a report from South Africa where a combination of radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) has been shown to result in a median survival of 5.7 months.[16] For advanced ESCC, fractionated high-dose-rate brachytherapy (18 Gy in 3 fractions or 16 Gy in 2 fractions on alternate days) has been shown to have the longest median survival of 7.1 months of dysphagia-free survival and 7.9 months overall median survival in south Africans.[17]

In contrast to the IARC estimates[4], we found lower age-standardized mortality rate for both sexes and among men i.e., 9.96 (7.63, 12.29) per 100,000 in the current study for both sexes compared to 11.8 per 100,000 by IARC [the 3rd highest in the East and Southern African region behind Malawi (16.7) and Kenya (12.0)] and among men a SMR of 10.08 per 100,000 in the current study compared to 15.8 per 100,000 (highest in the region) by IARC. For women, we found a higher ASMR of 9.64 per 100,000 compared to 8.6 per 100,000 as estimated by IARC.[4] The difference in the age-standardized mortality rates may be due to differences in research methods with the IARC using methods of incidence and mortality estimation

undertaken at the national level and hence their validity depends upon the representativeness and quality of information source from the national level which unfortunately are inadequate.[18]

We found being of high socioeconomic status compared to fair predicted longer overall survival while increasing age and being of low socioeconomic status predicted shorter overall survival. This data high lights the role played by social determinants contributing to ESCC mortality since socioeconomic status impacts on access to and use of clinical services.

Our results should be interpreted with some limitations in the context of a relatively small size and conduct in a single site therefore findings may not be extrapolated to the community. Second, a referral bias in that enrolment was in a referral hospital thus only ESCC patients who came to the hospital were enrolled. Lastly, less than 10% of participants had ESCC staging data as participants did not agree to performing staging tests after being told of ESCC diagnosis as this would add to the cost of care. However, we used the histological grading and evidence obstruction which suggest that the participants had advanced ESCC stages. Our study had multiple strengths. First, our data are complete with no losses to follow up, so these data are not affected by follow up or survival biases. This is important, since many cancer registries have no survival data due to the heighten losses to follow up. Second, our study was conducted in an ESCC high burden region of southwestern Uganda, which is an appropriate site for epidemiological study of ESCC.

In conclusion, the one-year incidence rates of all-cause mortality and age-standardized mortality rates among ESCC patients in rural Uganda is higher than has been reported. Future work should establish if these rates change with improved access to chemoradiotherapy and longer follow up. Finally, in rural Uganda and similar settings with high ESCC burden, initiatives to improve access to oncology care should be prioritized to improve overall survival.

## **Declarations**

## **Ethics approval and consent to participate:**

The study procedures were approved by the Institutional Review Boards of Mbarara University of Science and Technology Research ethics committee (Protocol #07/11-16), Harvard TH Chan School of Public Health (Protocol #17-1086) and the Uganda National Council for Science and Technology (Protocol #HS37ES). All participants provided written informed consent in English or the local languages. Participants unable to read had a witness and used an inked fingerprint as signature. All methods were performed in accordance with the declaration of Helsinki.

## **Consent for publication:**

All authors consented to submission of the final manuscript.

## Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests:

None.

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## Authors' contributions:

SO, EBB, BAEL, SJA, ED, CKO, PO, WRM, DCC, and KEC contributed to the design of the study. SO, EBB, CKO, PO, and KEC carried out, analyzed, and interpreted the data. SO, EBB, BAEL, SJA, CKO, PO and KEC drafted the manuscript. All authors revised the manuscript critically for intellectual content and have read and approved the final manuscript.

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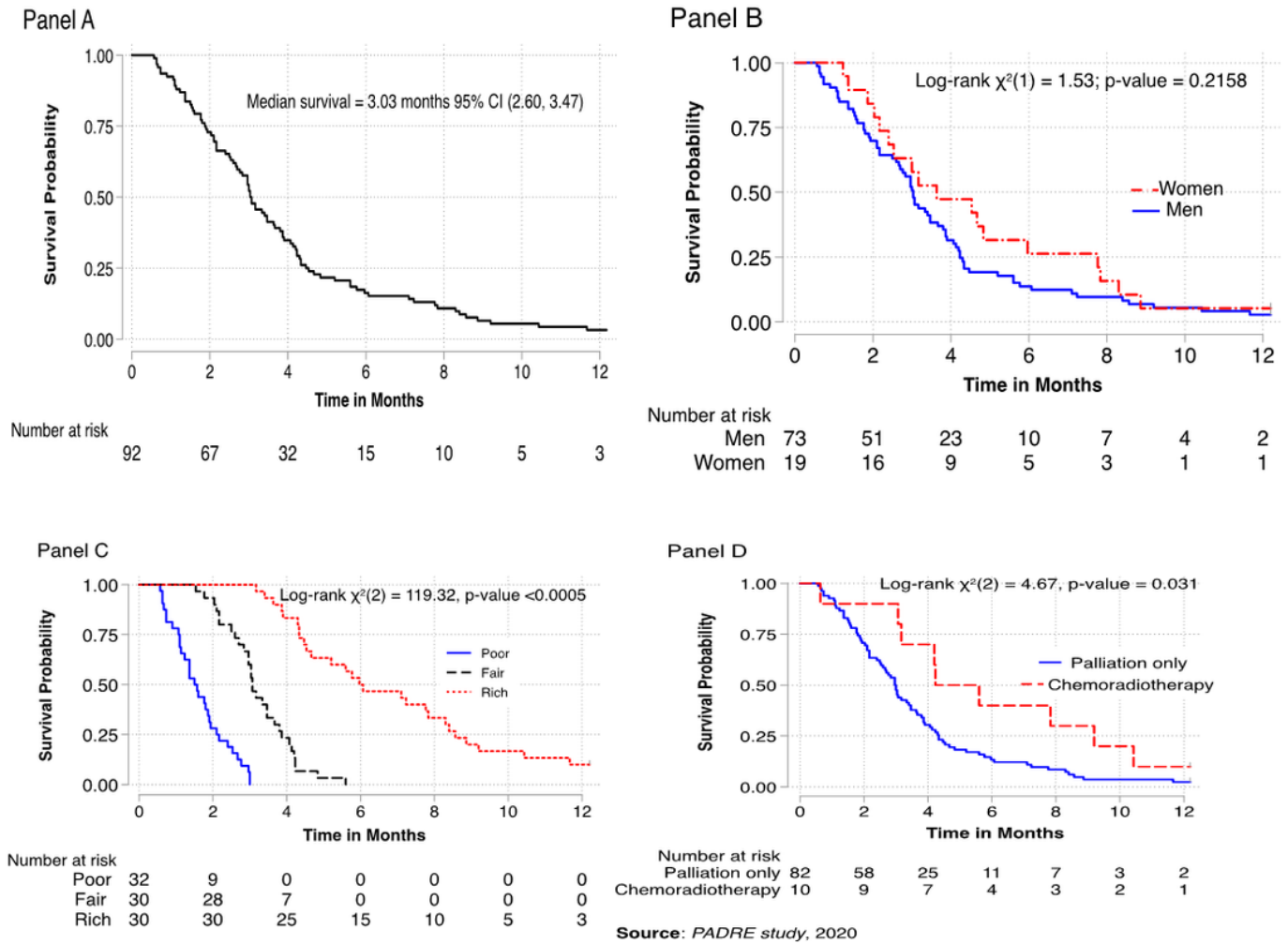
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## Figures



**Figure 1**

Kaplan-Meier curves showing overall survival from time of diagnosis for all participants (Panel A), by gender (Panel B), stratified by socioeconomic status (Panel C), and therapy (Panel D), PADRE study 2020