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Complications and Survivorship Trends After Primary Debulking Surgery for Ovarian Cancer

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Abstract

Background: We examined factors associated with postoperative complications, 1-year overall and cancer-specific survival after epithelial ovarian cancer (EOC) diagnosis.

Methods: Patients who underwent surgery for EOC between 2004 and 2013 were included. Multivariable models analyzed postoperative complications, overall survival, and cancer-specific survival.

Results: Among 5223 patients, surgical complications were common. Postoperative complications correlated with increased odds of overall and disease-specific survival at 1 y. Receipt of chemotherapy was similar among women with and without postoperative complications

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Disclosure

This study was conducted when the co-first author and corresponding author (Adan Z Becerra) was a PhD student at the University of Rochester and is now employed at Social & Scientific Systems, which was not involved with the study. Dr. Xu and Dr. Becerra contributed equally to this work and should be listed as co-first authors.

and was independently associated with a reduction in the hazard of overall and disease-specific death at 1-year. Extensive pelvic and upper abdomen surgery resulted in 2.26 times the odds of postoperative complication, but was associated with longer 1-year overall 0.53 (0.35, 0.82) and disease-specific survival 0.54 (0.34, 0.85).

Conclusions: Although extent of surgery was associated with complications, the survival benefit from comprehensive surgery offset the risk. Tailored surgical treatment for women with EOC may improve outcomes.

Keywords

Outcomes research; Ovarian neoplasms; Surgical procedures; Operative

Introduction

In the United States, over 22,000 new ovarian cancer cases and 14,070 deaths are expected yearly, making ovarian cancer the most lethal of the gynecologic cancers.¹ Most women present with advanced-stage disease where long-term survival is rare. Despite this poor overall prognosis, the combination of surgery and chemotherapy after diagnosis leads to high response rates. In the modern era, over half of women with stage III and IV ovarian cancer who have an initial complete response to therapy will survive longer than 5 y.²

Multiple randomized controlled clinical trials and observational studies have confirmed a survival benefit associated with complete cytoreduction at the time of initial ovarian cancer surgery. Resection of gross disease improves both progression-free and overall survival.^{3–8} Achieving optimal cytoreduction often requires incorporation of radical procedures such as en-bloc bowel resections, and upper abdominal surgery, which inherently increases both intraoperative, and short-term perioperative morbidity.⁹

Radical procedures performed at the time of ovarian cancer surgical debulking lead to high rates of postoperative complications.¹⁰ Despite these high rates of complications, most patients treated surgically for ovarian cancer can be supported through these events.¹¹ An increasing number of radical cytoreductive procedures are being performed in the United States and increasing centralization of ovarian cancer care may decrease the rate of complications over time.^{12,13}

Data evaluating the impact of postoperative complications on long-term cancer outcomes is limited. One of the challenges associated with high rates of perioperative complications is the potential for delayed (or even omitted) chemotherapy if deconditioning after surgery is significant.^{14,15} The aim of this study was to examine factors associated with postoperative complications, 1-year overall and cancer-specific survival after primary debulking surgery (PDS) for epithelial ovarian cancer independent of chemotherapy. Identification of patients who will die within the first year after radical surgery can potentially avert the futility of a highly morbid procedure. To estimate the longer-term effects of upfront treatment decisions and associated complications, we chose to focus on 1-year survival to capture a relevant period to evaluate the impact of surgery independent of chemotherapy received on cancer outcomes for women with ovarian malignancies.

Methods and materials

NYSCR and SPARCS

This study is a retrospective review of a data set utilizing the New York State Cancer Registry (NYSCR) and Statewide Planning and Research Cooperative System (SPARCS). The NYSCR has received the highest certification from the North American Association of Central Cancer Registries and has received Gold-Level certification since 1998 for data integrity.¹⁶ SPARCS is an all-payer hospital discharge database that contains patient-level data on all non-Veteran Affairs hospital admissions, ambulatory surgery procedures, and emergency department visits in New York State. Information on date and cause of death was obtained from NY State Vital Records and the National Death Index, which are linked to the NYSCR.

Study cohort selection

Patients with a primary diagnosis of stage III or IV ovarian cancer, as determined by the International Federation of Gynecology and Obstetrics (FIGO), between January 1, 2004, and December 31, 2013, were identified from the NYSCR and SPARCS. Ovarian cancer was defined using SEER site codes C561-C569 and SEER site recode 27040. The cohort was limited to those who had undergone oophorectomy with or without debulking as primary treatment of ovarian cancer. Non-epithelial and mucinous histology were excluded due to the distinct biologic behavior of these neoplasms. Patients with missing data were excluded from analysis to maintain the consistency of cohort characteristics across all analyses. 1760 patients were excluded for nonepithelial and mucinous histology, 477 were excluded for missing staging data, 502 were excluded for missing chemotherapy data, 326 were excluded for missing demographics, and 2780 patients were excluded for having stage I or II disease (Figure).

Definition of outcomes

The primary outcomes of the study were postoperative complication within 30-days of surgery, 1-year overall mortality, and 1-year ovarian cancer-specific mortality. Survival data were available through December 31, 2014, and survival days were calculated from the date of surgery to the date of death. Patients were either censored at 1 y or on December 31, 2014, whichever came first. For cancer-specific mortality, patients who died from nonovarian cancer causes were censored at the time of death.

Additional covariates

Patient factors considered for analyses included age, which was considered a continuous variable, insurance type, unscheduled admission, and Elixhauser comorbidities identified as present on admission during the index admission as well as any inpatient admission in the prior year to maximize the capture rate.¹⁷ Oncologic factors included FIGO stage, histology, and receipt of chemotherapy. Operative factors included year of surgery and extent of surgery. The extent of surgery was classified into three categories based on resection of other organs: simple pelvic (SP), extensive pelvic (EP), extensive upper abdominal (EU), or extensive pelvic and upper abdominal (EPEU). EP included small bowel resection,

rectosigmoid resection, colectomy, or cystectomy. Patients were classified as EU if they underwent a splenectomy, pancreatectomy, cholecystectomy, hepatectomy, or diaphragm resection. All other patients were classified as SP.

Hospital characteristics included academic status, location, and annual ovarian cancer resection volume. Academic status and location were obtained by merging the data set with data from the American Hospital Association Annual Survey. Based on the distribution of the data, annual hospital ovarian cancer resection volume was characterized into the following categories: low (0–17 cases per year), medium (18–52 cases per year), and high (> 53 cases per year). Patients with missing data for any covariates or outcomes of interest were excluded from analysis.

Statistical analysis

Bivariate analysis was performed using Student *t*-test and chi-square test wherever appropriate. Two-level mixed-effects multivariable analyses were used to account for clustering of patients among hospitals. Models included covariates examined in bivariate analysis as well as the unique hospital identifier as a clustering variable. Logistic regression analysis was used for the outcome of postoperative complication, Cox proportional hazards analysis was used for 1-year overall mortality, and competing-risks analysis was used for 1-year ovarian cancer-specific mortality analysis. Logistic regression analysis was performed using package MCMCglmm¹⁸ Cox proportional hazards analysis was performed using package coxme,¹⁹ and competing-risk analyses were performed using package frailtypack in R, Version 3.2.1 (R Foundation for Statistical Computing).²⁰ All other analyses were performed in SAS, Version 9.4 (SAS Institute, Cary, NC). The study was approved by the University of Rochester Medical Center (IRB #00054886) and New York Department of Health (DPRB #1412–05) institutional review boards.

Results

A total of 11,068 women underwent ovarian cancer resection of which 5223 patients met inclusion criteria. Patient characteristics are presented in Table 1. The median age of the cohort was 62 y with an interquartile range of 52–73 y. Eighty-five percent of the cohort was white and 9% was black. Forty-eight percent had Medicaid insurance. Most of the patients were stage III (61%) and had serous histology (76%). Sixty-eight percent of the patients underwent SP resection and 79% received postoperative chemotherapy.

Postoperative complications

Rates of the complications are presented in Table 2. 26.1% of the cohort had at least one postoperative complication within 30 d of surgery. Thirty-day mortality was 3.0%. In bivariate analyses (Table 1), factors associated with complications were age, black race, Medicaid insurance, higher comorbidity burden, unscheduled admission, stage IV disease, and extensive resection. Specific comorbidities associated with postoperative complications included congestive heart failure, chronic obstructive pulmonary disease (COPD), renal failure, and obesity ($P < 0.05$) on bivariate analysis. Length of stay was increased and ICU stay was more common after a complication. Receipt of chemotherapy was similar between

patients who experienced a complication and those who did not. After controlling for patient, oncologic, and hospital characteristics, independent factors that remained associated with complications included COPD, obesity, extensive surgery, and treatment at a medium-volume hospital (Table 3).

Reported complications increased during the study period. In 2006–2007, the risk of a postoperative complication was increased (HR = 1.61, 95% CI 1.28, 2.13) compared with the risk in 2004–2005 (referent). This risk was 2.08 (95% CI 1.58, 2.74) times in 2008–2009; 2.32 (95% CI 1.67, 3.16) times in 2010–2011; and 2.51 (95% CI 1.81, 3.42) in 2012–2013.

One-year overall and cancer-specific mortality survival

Of patients with a postoperative complication, 77.2% were alive at 1 y, compared with 89% of patients without a complication ($P < 0.01$). Factors associated with 1-year overall mortality after controlling for patient, oncologic, and hospital characteristics include age, Medicaid insurance, emergency surgery, ICU stay, stage IV disease, clear cell histology, and postoperative complication (Table 3). COPD and renal failure were associated with 1-year mortality but not cancer-specific mortality. Receipt of chemotherapy was strongly associated with improved disease-specific and overall survival at 1 y.

Despite the strong association between extent of resection and complications, overall extensive surgery improved survival at 1 y (Table 3). Patients who underwent EPEU surgery had lower risk of 1-year overall and disease-specific mortality compared with patients who only had SP surgery (HR = 0.53, 95% CI = 0.35, 0.82 and 0.54 (0.34, 0.85), respectively). Complications increased mortality at 1 y from 10.2% to 23.2% in patients treated with SP surgery; and from 5.9% to 10.3% for patient treated with EPEU.

Discussion

In this study, specific surgical risk factors were evaluated for correlation to perioperative complications and 1-year mortality for women undergoing PDS for ovarian cancer. Our results demonstrate increased rates of complications for older women, women with medical comorbidities, stage IV disease, and those treated with more extensive surgery. As surgery became more aggressive, the risk of complications increased. Despite higher rates of complications, more extensive surgery was inversely related with both 1-year overall mortality and 1-year cancer-specific mortality. Even among patients who experienced complications, those with extensive surgery had similar survival rates compared with those with simple surgery without complications.

Although modern perioperative support can mitigate the effects of many medical comorbidities, the results of this study corroborate the known impact of medical comorbidities on oncologic outcomes from ovarian cancer.^{11,21} Comorbidities are well-described as prognostic indicators for women with advanced ovarian cancer.^{10,21–24} A negative association between 1- and 5- year survival rates and the number of patient comorbidities has been demonstrated.²¹ Specific comorbidities influencing survival include thromboembolism, hematologic complications, and infections.²³

Clarifying which patient, hospital, and oncologic characteristics should tailor treatment plans to individual patients remains a significant clinical question for the care of women with ovarian cancer. Maximum cytoreduction has been the foundation of ideal treatment for advanced ovarian carcinoma since as early as Meigs' 1934 study, in which he recommended that surgeons aggressively remove as much tumor as possible to improve survival.²⁵ Multiple subsequent studies have since verified this clinical observation.³⁻⁸ The trade off to more extensive surgery is an increase in complications. Complication rates observed in this study mirror those reported in previous publications. High complication rates with PDS have led to a recent questioning of the surgical dogma of upfront maximum surgical cytoreduction in this disease, particularly with two recent prospective trials of neoadjuvant chemotherapy (NACT) that revealed no survival difference compared to PDS.^{26,27} The complex interplay between patient characteristics, tumor biology, and surgical effort and timing was highlighted in a recent analysis of the National Cancer Database where improved outcomes for patients treated with PDS were demonstrated compared with patients treated with NACT.¹⁴ The statistical significance disappeared when normalized for performance status, suggesting that performance status and comorbidities may confound survival rates seen in NACT studies.¹⁴

Older age impacts outcomes from ovarian cancer with increased age leading to more perioperative complications and higher mortality compared with younger women after PDS.²⁸⁻³⁰ In this study, age increased the rate of postoperative complications within 30 d of surgery, and led to higher 1-year overall and cancer-specific mortality. Although this disparity in mortality risk may result from older patients receiving less-optimal surgical and medical treatment than younger patients, the age of the patient should be considered in the selection of surgical treatments for ovarian cancer.³⁰ There is a complex interplay between age, comorbidities, treatment administration, and cancer outcomes which we were not able to tease out in this secondary data analysis.

We assessed ovarian cancer 1-year mortality to best describe the impact of surgery on the treatment course of this disease. The morbidity associated with ovarian cancer surgery is generally reported as 30-day mortality.³¹ This short-term outcome measurement potentially misses the benefits of more extensive surgery, particularly as the vast majority of patients experiencing complications can be supported through the postoperative period.¹¹ Evaluating surgical outcomes with 5-year mortality as the endpoint may be biased by mediating factors associated with chemotherapy and tumor biology. Because ovarian cancer is uniquely chemotherapy-sensitive among the solid tumors, measuring the impact of ideal surgery on this group of women is therefore challenging, especially as chemotherapy efficacy and options have improved over time. One-year survival has been previously used as an endpoint in a Danish registry study of patients with ovarian cancer. Results in that study were similar to ours; factors associated with survival included medical comorbidities, advanced stage, and increased age.³²

The demonstration that the extent of surgery improved 1-year survival despite an increase in complications challenges the value of our current surgical quality measures. Medicare's "Hospital Compare" and other hospital ranking websites evaluate only 30-day mortality. An examination of the Medicare Provider Analysis and Review File from 2011 to 2013 recently

demonstrated an inverse relationship between CMS hospital star rating and short-term cancer outcomes across cancer types.³³ Specific to ovarian cancer, a longer period (90 d) for the evaluation of postoperative morbidity and mortality has been shown to better differentiate surgical quality than a 30-day window.³⁴

The New York state tumor registry provides rich and granular population level information on practice patterns in ovarian cancer. The large number of patients with detailed information regarding comorbidities and complications is a strength of this study. However, there are limitations of this study as well as restrictions of available data inherent to any data set. Hospital discharge databases are limited in their ability to capture accurate medical comorbidities. Specific complications may have impacted survival differently compared with others, but we were only interested in adjusting for the confounding effects of any complication to estimate an unbiased effect of surgery as opposed to individual effects of complications. Evaluating the individual effects of complications was beyond the scope of the study because we only adjusted for it as a confounder and was not our main exposure variable of interest. The specifics of chemotherapy administered were also unavailable. The increasing complication rates that were seen over time may have been related to increasingly detailed reporting. Variations in practice patterns between providers, institutions, and reporting accuracy over time were difficult to adjust for. This type of study is unable to assess the impact of complications of health-related quality of life, which is certainly impacted by surgical complications. Furthermore, as is the case with every observational study, there is a change that selection bias and unobserved confounding could be explaining the results. For example, patients with unresectable or more complicated tumors might have only received SP surgery. We attempted to mitigate this risk by adjusting for an important array of potential confounders including patient, treatment, and oncologic factors (such as stage) and also by adjusting for clustering of outcomes using multilevel modeling.

In conclusion, despite leading to higher rates of complications, more aggressive surgery improved overall and disease-specific survival for women diagnosed with ovarian cancer. Despite the higher short-term complication rates, these data reaffirm the long-term benefits of optimal surgery for patients including improved disease-free and overall survival at 1 y. In addition, our findings suggest the need for “precision medicine” in matching the right patient with the right surgery at the correct time during her treatment course for this disease in addition to best perioperative practices. Individualized surgical treatment plans for women with ovarian cancer should reflect the patient’s medical comorbidities, oncologic characteristics, age, and available surgical support within an institution. Further research on this decision-making and prospective measurement of patient outcomes is needed.

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Fig –.
Selection criteria for study cohort. (Color version of figure is available online.)

Table 1 –

Bivariate analysis by complication.

Patient factors	Postoperative complication (<i>n</i> = 1363, 26.1%)	No postoperative complication (<i>n</i> = 3860, 73.9%)	<i>P</i> -value
Age (Med, IQR)	64 (55–73)	61 (52–70)	<0.0001
Race			0.03
White	1125 (82.5)	3307 (85.7)	
Black	150 (11.0)	328 (8.5)	
Other	88 (6.5)	225 (5.8)	
Medicaid insurance	768 (56.4)	1763 (45.7)	<0.0001
Comorbidities			
Hypertension	489 (35.9)	1482 (38.4)	0.10
Congestive heart failure	51 (3.7)	61 (1.6)	<0.0001
Diabetes mellitus	138 (10.1)	386 (10.0)	0.90
Chronic obstructive pulmonary disease	175 (12.8)	382 (9.9)	0.003
Peripheral vascular disease	16 (1.2)	29 (0.8)	0.15
Renal failure	37 (2.7)	39 (1.0)	<0.0001
Liver disease	20 (1.5)	55 (1.4)	0.90
Obesity	95 (7.0)	203 (5.3)	0.02
Unscheduled admission	472 (34.6)	805 (20.9)	<0.0001
Intensive care unit	273 (20.0)	467 (12.1)	<0.0001
Length of stay (Med, IQR)	11 (7–18)	5 (4–8)	<0.0001
FIGO stage			<0.0001
III	732 (53.7)	2438 (63.2)	
IV	631 (46.3)	1422 (36.8)	
Histology			0.02
Adenocarcinoma	1058 (77.6)	2913 (75.5)	
Endometrial	44 (3.2)	2014 (5.3)	
Clear cell	47 (3.5)	147 (3.8)	
Other	214 (15.7)	596 (15.4)	
Operative approach			<0.0001
Open	1326 (97.3)	3638 (94.3)	

Patient factors	Postoperative complication (n = 1363, 26.1%)	No postoperative complication (n = 3860, 73.9%)	P-value
Minimally invasive	37 (2.7)	222 (5.7)	<0.0001
Year of surgery			
2004–2005	231 (17.0)	907 (23.5)	
2006–2007	311 (22.8)	815 (21.1)	
2008–2009	291 (21.3)	749 (19.4)	
2010–2011	285 (20.9)	753 (19.5)	
2012–2013	245 (18.0)	636 (16.5)	
Surgical extent			<0.0001
Simple pelvic	724 (53.1)	2819 (73.0)	
Extensive pelvic	423 (31.0)	715 (18.5)	
Extensive upper abdomen	71 (5.2)	157 (4.1)	
Extensive pelvic & extensive upper abdomen	145 (10.6)	169 (4.4)	
Receipt of chemotherapy	1014 (74.4)	3115 (80.7)	<0.0001
Academic center	748 (54.9)	2133 (55.3)	0.81
Location			0.41
Urban	1352 (99.2)	3819 (98.9)	
Rural	11 (0.8)	41 (1.1)	
Annual ovarian cancer resection volume			0.61
Low	376 (27.6)	1044 (27.0)	
Medium	451 (33.1)	1239 (32.1)	
High	536 (39.3)	1577 (41.9)	
1-Year survival	1062 (77.2)	3491 (89.0)	<0.0001

Table 2 –

Description of major complications n (%).

Surgical site infection	220 (4.2)
Abdominal abscess	115 (2.2)
Sepsis	141 (2.7)
Pneumonia	88 (1.7)
Pulmonary failure	411 (7.9)
Myocardial infarction	32 (0.6)
Venous thromboembolism	153 (2.9)
Acute renal failure	141 (2.7)
Gastrointestinal bleeding	17 (0.0)
Hemorrhage	108 (2.1)

Table 3 –

Factors associated with postoperative complications and 1-year mortality.

	Postoperative complication [OR (95% CI)]	1-Year overall mortality [HR (95% CI)]	1-Year ovarian cancer-specific mortality [HR (95%CI)]
Age (per year)	1.01 (0.99, 1.02)	1.03 (1.02, 1.04)	1.03 (1.02, 1.04)
Race			
White	Reference	Reference	Reference
Black	1.04 (0.78, 1.38)	1.37 (1.09, 1.74)	1.25 (0.95, 1.65)
Other	1.16 (0.81, 1.65)	1.02 (0.70, 1.50)	0.89 (0.57, 1.39)
Medicaid insurance	0.97 (0.78, 1.19)	1.18 (0.96, 1.45)	1.06 (0.84, 1.33)
Comorbidities			
Hypertension	0.85 (0.72, 1.04)	0.90 (0.76, 1.06)	0.87 (0.72, 1.04)
Congestive heart failure	1.02 (0.57, 1.73)	1.22 (0.89, 1.70)	1.31 (0.89, 1.91)
DM	1.02 (0.77, 1.35)	1.16 (0.92, 1.45)	1.19 (0.92, 1.55)
COPD	1.42 (1.10, 1.83)	1.34 (1.08, 1.65)	1.23 (0.96, 1.58)
Peripheral vascular disease	1.25 (0.49, 2.74)	0.90 (0.46, 1.75)	0.98 (0.46, 2.09)
Renal failure	1.58 (0.90, 2.82)	1.50 (1.01, 2.23)	1.27 (0.78, 2.07)
Liver disease	0.80 (0.40, 1.59)	1.59 (0.93, 2.71)	1.43 (0.76, 2.69)
Obesity	1.56 (1.14, 2.17)	0.97 (0.70, 1.35)	1.02 (0.71, 1.48)
Scheduled admission	1.49 (1.18, 1.85)	0.67 (0.57, 0.79)	0.72 (0.60, 0.87)
ICU	1.41 (1.11, 1.82)	1.33 (1.11, 1.60)	1.39 (1.13, 1.70)
LOS (per 1 d)	1.19 (1.17, 1.21)	1.03 (1.02, 1.03)	1.03 (1.02, 1.04)
FIGO stage			
III	Reference	Reference	Reference
IV	1.08 (0.92, 1.30)	1.61 (1.39, 1.87)	1.62 (1.39, 1.90)
Histology			
Adenocarcinoma	Reference	Reference	Reference
Endometrial	0.63 (0.41, 0.95)	1.40 (0.98, 2.00)	1.40 (0.93, 2.09)
Clear cell	1.01 (0.66, 1.55)	3.39 (2.54, 4.53)	3.69 (2.70, 5.04)
Other	0.98 (0.79, 1.24)	1.92 (1.62, 2.29)	1.76 (1.44, 2.15)
Operative approach			
Open	Reference	Reference	Reference

	Postoperative complication [OR (95% CI)]	1-Year overall mortality [HR (95% CI)]	1-Year ovarian cancer-specific mortality [HR (95% CI)]
Minimally invasive	0.68 (0.43, 1.05)	0.70 (0.45, 1.09)	0.74 (0.46, 1.21)
Surgical extent			
Simple pelvic	Reference	Reference	Reference
Extensive pelvic	1.34 (1.10, 1.66)	1.04 (0.88, 1.23)	1.02 (0.84, 1.24)
Extensive upper abdomen	1.49 (1.00, 2.21)	0.63 (0.39, 1.03)	0.60 (0.34, 1.05)
Extensive pelvic + extensive upper abdomen	2.26 (1.57, 3.21)	0.53 (0.35, 0.82)	0.54 (0.34, 0.85)
Year of surgery			
2004–2005	Reference	Reference	Reference
2006–2007	1.61 (1.28, 2.13)	1.04 (0.86, 1.27)	1.11 (0.88, 1.41)
2008–2009	2.08 (1.58, 2.74)	1.00 (0.81, 1.24)	1.03 (0.80, 1.33)
2010–2011	2.32 (1.67, 3.16)	0.73 (0.57, 0.94)	1.00 (0.77, 1.30)
2012–2013	2.51 (1.81, 3.42)	0.57 (0.43, 0.76)	0.74 (0.55, 1.00)
Receipt of chemotherapy	0.95 (0.77, 1.17)	0.34 (0.29, 0.40)	0.39 (0.33, 0.47)
Postoperative complication	N/A	1.43 (1.21, 1.69)	1.45 (1.21, 1.75)
Annual ovarian cancer resection volume			
Low	Reference	Reference	Reference
Medium	1.39 (1.04, 1.87)	1.06 (0.87, 1.29)	1.13 (0.90, 1.41)
High	1.01 (0.71, 1.58)	1.10 (0.89, 1.35)	1.19 (0.95, 1.48)
Major academic	0.96 (0.69, 1.32)	0.99 (0.85, 1.16)	1.02 (0.86, 1.22)
Urban hospital	1.21 (0.50, 3.36)	0.58 (0.34, 0.99)	0.51 (0.28, 0.94)