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Public health insurance and cancer-specific mortality risk among patients with breast cancer: A prospective cohort study in China

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Abstract

Little is known about how health insurance policies, particularly in developing countries, influence breast cancer prognosis. Here, we examined the association between individual health insurance and breast cancer-specific mortality in China. We included 7436 women diagnosed with invasive breast cancer between 2009 and 2016, at West China Hospital, Sichuan University. The health insurance plan of patient was classified as either urban or rural schemes and was also categorized as reimbursement rate (ie, the covered/total charge) below or above the median. Breast cancer-specific mortality was the primary outcome. Using Cox proportional hazards models, we calculated hazard ratios (HRs) for cancer-specific mortality, contrasting rates among patients with a rural insurance scheme or low reimbursement rate to that of those with an urban insurance scheme or high reimbursement rate, respectively. During a median follow-up of 3.1 years, we identified 326 deaths due to breast cancer. Compared to patients covered by urban insurance schemes, patients covered by rural insurance schemes had a 29% increased cancer-specific mortality (95% CI 0%-65%) after adjusting for demographics, tumor characteristics and treatment modes. Reimbursement rate below the median was associated with a 42% increased rate of cancer-specific mortality (95% CI 11%-82%). Every 10% increase in the reimbursement rate is associated with a 7% (95% CI 2%-12%) reduction in cancer-specific mortality risk, particularly in patients covered by rural insurance schemes (26%, 95% CI 9%-39%). Our findings suggest that underinsured patients face a higher risk of breast cancer-specific mortality in developing countries.

Abbreviations: BCIMS, Breast Cancer Information Management System; BMI, body mass index; CIs, confidence intervals; HER2, human epidermal growth factor receptor 2; HR, hazard ratios; NRCMS, New Rural Cooperative Medical Scheme; OR, odds ratio; SES, socioeconomic status; UEBMI, Urban Employee-based Basic Medical Insurance Scheme; URBMI, Urban Resident-based Basic Medical Insurance Scheme; WCH, West China Hospital.

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1 | INTRODUCTION

Battling cancer is a crushing burden for all patients, but particularly so for those who are vulnerable to financial stress. It is common that cancer patients experience severe financial stress throughout their survivorship,[1] especially in developing countries where the health system is not ready to ease the burden for everyone. Cancer patients have higher out-of-pocket costs and may be absent from work for quite a while, which further lowers the ability to pay for medical care.[1,2] As an avalanche of "financial toxicity"—the damaging economic side effects of illness, cancer patients are at tremendous risk for debt, bankruptcy and impaired psychological wellbeing.[3,4]

It is well-documented that social inequality in health contributes to the disparities in cancer survivorship in both developed and developing countries, including China.[5-8] The presence of a public health insurance system seems essential for a country to achieve universal healthcare coverage and health equity.[9] Improved health insurance coverage can reduce sociodemographic disparities in cancer care, including breast cancer, through early diagnosis and optimal treatment.[10,11] Fewer studies have paid attention to the impact of health insurance on cancer prognosis. So far, four US studies,[11-14] support the hypothesis that underinsured patients have a worse breast cancer prognosis, but two other studies from Australia and Brazil reported no clear differences related to the level of health insurance.[15,16] However, it is largely unclear whether the health insurance policies particularly in developing countries, where the patients may face higher financial toxicity, influence breast cancer prognosis. Moreover, all reports have focused on insurance status or types, while no studies have addressed the out-of-pocket cost as an important barrier to cancer care.[11-16] It is, therefore, of critical importance to understand how different insurance plans, featured by varying reimbursement rates (ie, the covered/total charge) within specific insurance type, further contribute to the disparities in diagnosis, treatment and prognosis of breast cancer.

The health insurance system was first introduced to China mainland China in 1980s, and drastically expanded to over 95.7% of the total population over the past decades.[17,18] The majority of insurance system is state-run, while commercial insurance may be purchased as a complement. There are three major state-run schemes of public health insurance in China, including the new rural cooperative medical scheme (NRCMS, covering the residents of rural households and launched in 2003), urban resident-based basic medical insurance scheme (URBMI, covering the unemployed, children and elderly and launched in 2007) and urban employee-based basic medical insurance scheme (UEBMI, covering employees and launched in 1998).[17,18] A variety of medical expenditures could be reimbursed by the public health insurance, and the rest of costs would be paid out of pocket or by commercial insurance, if any. These costs include, for example, deductible, coinsurance and certain medical examinations (eg, positron-emission tomography-computed tomography) and treatment (eg, trastuzumab until the year of 2018 and CDK4/6 inhibitors).

Leveraging a prospective large-scale cohort of patients with invasive breast cancer in China diagnosed from 2009 to 2016, we aimed to examine the associations of health insurance types and reimbursement rates with the risks of breast cancer-specific mortality.

What's new?

Although improved health insurance coverage can reduce sociodemographic disparities in cancer care, the impact of health insurance on cancer prognosis is unclear. In a prospective cohort of breast cancer patients in China, under-insured patients (insured by rural schemes or with low reimbursement rate) were at increased risk of cancer-specific mortality, independent of tumor characteristics and primary treatment. Promoting public health insurance, particularly reimbursement rate, in developing countries may help reduce disparities in breast cancer survivorship.

2 | MATERIALS AND METHODS

2.1 | Study population

We identified 7623 female patients who were diagnosed with invasive breast cancer at West China Hospital (WCH), Sichuan University from January 1, 2009, to December 31, 2016, based on the Breast Cancer Information Management System (BCIMS). The BCIMS covers virtually all patients with breast cancer diagnosed at WCH since 2008 and prospectively collects information on demographic and clinical characteristics, laboratory examinations, treatment and follow-up visits.[18] We excluded 37 male patients, three patients due to loss to follow-up and 147 patients without the information on both types of health insurance and reimbursement rate, leaving 7436 patients in the final cohort.

2.2 | Health insurance

Three insurance schemes are administered by different national institutions and operated by local governments. NRCMS is administered by the Chinese National Health and Family Planning Commission and financed at the county level, while URBMI and UEBMI are administered by the Chinese Ministry of Human Resources and Social Security and financed at the municipal (prefecture) level in 2013.[19] Thus, the benefit packages and financial support are fragmented and inequitable across the schemes. For example, compared to UEBMI and URBMI, NRCMS is limited to a lower reimbursement cap and covers a narrower spectrum of diseases. The mean reimbursement rate for NRCMS is mainly 50% to 65%, which is much lower than UEBMI with a rate of 85% to 95%.[20,21] The disparities between urban and rural health insurances are thus considerable. Therefore, China has been establishing a consolidated health insurance scheme by 2020. For example, the fund pooling and management of NRCMS (from county level) and UEBMI and URBMI (from municipal level) should be moved to provincial and then country levels. The reimbursement rate is defined as the amount of medical expenses covered by insurance divided by the total expense. As the insurance is partly funded by local governments, the reimbursement rates may vary widely across counties, even under the same insurance scheme. Moreover, the rate is individual-based, affected and calculated by age, years of employment, hospital level and treatment modes.

The information on insurance types and reimbursement rates (for the primary treatment) is routinely documented in BCIMS. Specifically, the information on the type of insurance is provided by patients at the registration to BCIMS, while the rate of reimbursement is collected for the primary treatment during follow-up. Given the different administrations and insurance plans (Supporting Information Material), we classified insurance types into urban (ie, URBMI, UEBMI, and/or commercial insurances) and rural (ie, NRCMS) schemes, respectively. In the analysis of insurance type, 139 patients without any insurance and eight patients of unknown insurance status were excluded. Our data showed that the reimbursement rate was different among patients insured by urban or rural schemes (Figure S1). We also classified patients by reimbursement rate below (0-69%) or above (70%-100%) the median. Patients without insurance were coded as 0 reimbursement rate. Then, 569 patients (192 insured by rural schemes) were excluded from this analysis due to unknown reimbursement rate.

2.3 | Breast cancer-specific and overall mortality

All patients were actively followed through telephone contact and medical visits until death or May 17, 2017, whichever came first. The underlying cause of death was ascertained from the medical records, whenever possible, or informed by the immediate family members. We studied breast cancer-specific mortality as the primary outcome and overall mortality as the secondary outcome.

2.4 | Statistical analysis

First, we described the demographic and clinical characteristics among patients with different insurance types and reimbursement rates. Demographic and clinical characteristics were obtained from BCIMS and classified as showed in Table 1. We examined the associations of health insurance type and reimbursement rate with different treatment modes, using logistic regression with adjustment for demographic and clinical characteristics. To account for correlations between treatment types, we additionally adjusted for other types of treatment.

We examined the associations of health insurance type and reimbursement rate with different treatment modes, using logistic regression with adjustment for demographic and clinical characteristics. To account for correlations between treatment types, we additionally adjusted for other types of treatment.

Next, we calculated and plotted the cumulative rates and 95% confidence intervals (CIs) of breast cancer-specific and overall mortality by insurance type and reimbursement rate up to 5 years after cancer diagnosis using a competing risk model.[21] Hazard ratios (HRs) and 95% CIs of breast cancer-specific and overall mortality were then estimated from Cox regression by contrasting patients insured by the rural scheme to patients insured by the urban scheme, as well as patients with low reimbursement rate to those with high. The proportional hazards assumption, tested based on Schoenfeld residuals, was not violated. To illustrate the joint effect of insurance type and reimbursement rate, we further examined the association of every 10% increase in reimbursement rate with mortality risks by insurance type.

In Model A, we adjusted for demographic factors, including age (as a continuous variable), calendar year at diagnosis, ethnic group, educational level (as a proxy for socioeconomic status, SES) and marital status. In Model B, we additionally adjusted for clinical characteristics (as potential mediators), including comorbidity, histological type, tumor stage, hormone receptor status (including both estrogen and progesterone receptors), HER2 status and Ki-67 level. In Model C, we additionally controlled for treatment modes, namely surgery, chemotherapy, radiotherapy, hormonal therapy and trastuzumab therapy. Age was treated as continuous variables, whereas other covariates were categorized as showed in Table 1.

Because body mass index (BMI) would be neither the cause nor consequence of different insurances, we did not adjust for it in the primary analysis. We, however, noted that patients with different insurance were characterized by different BMI. We, therefore, performed an additional analysis by adjusting for BMI at diagnosis. According to the recommendation for Asian populations,[22] we classified BMI into $<23\ kg/m^2$ (nonoverweight) and $\geq 23\ kg/m^2$ (overweight). SES and accessibility to medical service are highly correlated with individual insurance plans. To further disentangle the potential influence of SES and accessibility to health-care, we performed a sensitivity analysis by clustering patients residing in the same community/county through the zip code of residence.

All analyses were performed in STATA statistical software (version 14; STATA, College Station, Texas). Value of $P < .05$ indicated statistical significance.

TABLE 1 Characteristics of patients with invasive breast cancer by insurance type and reimbursement rate

		By insurance type			By reimbursement rate		
	All (n = 7436) n (%)	Urban schemes (n = 5327) n (%)	Rural schemes (n = 1962) n (%)	*P*	70%-100% (n = 3588) n (%)	0%-69% (n = 3279) n (%)	*P*
Age at diagnosis, years				.05			.05
18-39	1276 (17.2)	876 (16.4)	365 (18.6)		581 (16.2)	580 (17.7)	
40-49	3145 (42.3)	2102 (39.5)	975 (49.7)		1414 (39.4)	1517 (46.3)	
≥50	3015 (40.6)	2349 (44.1)	622 (32)		1593 (44.4)	1182 (36.0)	
Calendar year at diagnosis				.05			.05
2009-2012	3419 (46.0)	2485 (46.7)	853 (43.5)		1514 (42.2)	1588 (48.4)	
2013-2016	4017 (54.0)	2842 (53.3)	1109 (56.5)		2074 (57.8)	1691 (51.6)	
Ethnic groups				.05			
Han	7278 (97.9)	5228 (98.1)	1909 (97.3)		3527 (98.3)	3197 (97.5)	
Minority	155 (2.1)	97 (1.8)	53 (2.7)		60 (1.6)	81 (2.4)	
Unknown	3 (0.1)	2 (0.1)	0 (0.0)		1 (0.1)	1 (0.1)	
Education (years)				.05			.05
≤6	1326 (17.8)	587 (11.0)	707 (36.0)		389 (10.8)	799 (24.4)	
7-9	2739 (36.8)	1689 (31.7)	986 (50.2)		1091 (30.4)	1428 (43.6)	
10-12	1583 (21.3)	1359 (25.5)	200 (10.2)		878 (24.5)	594 (18.1)	
>12	1763 (23.7)	1671 (31.4)	68 (3.5)		1219 (34.0)	450 (13.7)	
Unknown	25 (0.4)	21 (0.4)	1 (0.1)		11 (0.3)	8 (0.2)	
Marital status				.05			
Married	7253 (97.5)	5168 (97.0)	1942 (98.9)		3490 (97.3)	3208 (97.8)	
Nonmarried	183 (2.5)	159 (3.0)	20 (1.1)		98 (2.7)	71 (2.2)	
BMI, kg/m^2				.05			.05
<23	3806 (51.2)	2869 (53.9)	870 (44.3)		1943 (54.2)	1591 (48.5)	
≥23	3602 (48.4)	2440 (45.8)	1085 (55.3)		1633 (45.5)	1680 (51.3)	
Unknown	28 (0.4)	18 (0.3)	7 (0.4)		12 (0.3)	8 (0.2)	
Menopausal status				.05			.05
Premenopausal	4523 (60.8)	3054 (57.3)	1361 (69.4)		2028 (56.5)	2146 (65.5)	
Postmenopausal	2893 (38.9)	2258 (42.4)	597 (30.4)		1554 (43.3)	1126 (34.3)	
Unknown	20 (0.3)	15 (0.3)	4 (0.2)		6 (0.2)	7 (0.2)	
Comorbidity				.05			.05
No	6719 (90.4)	4786 (89.8)	1803 (91.9)		3220 (89.7)	2985 (91.0)	
Yes	717 (9.6)	541 (10.2)	159 (8.1)		368 (10.3)	294 (9.0)	
Hormone receptor status							.05
Negative	1867 (25.1)	1323 (24.8)	516 (26.3)		835 (23.3)	887 (27.1)	
Positive	5229 (70.3)	3747 (70.3)	1372 (69.9)		2608 (72.7)	2257 (68.8)	
Unknown	340 (4.6)	257 (4.9)	74 (3.8)		145 (4.0)	135 (4.1)	
HER2 status				.05			.05
Negative	4155 (55.9)	3033 (56.9)	1047 (53.4)		2060 (57.4)	1793 (54.7)	
Positive	1680 (22.6)	1183 (22.2)	460 (23.4)		811 (22.6)	762 (23.2)	
Unknown	1601 (21.5)	1111 (20.9)	455 (23.2)		717 (20.0)	724 (22.1)	
Ki-67 level				.05			.05
<14%	1301 (17.5)	975 (18.3)	296 (15.1)		665 (18.5)	541 (16.5)	
≥14%	5507 (74.1)	3906 (73.3)	1501 (76.5)		2673 (74.5)	2457 (74.9)	
Unknown	628 (8.5)	446 (8.4)	165 (8.4)		250 (7.0)	281 (8.6)	

(Continues)

TABLE 1 (Continued)

	All (n = 7436) n (%)	By insurance type			By reimbursement rate		
		Urban schemes (n = 5327) n (%)	Rural schemes (n = 1962) n (%)	*P*	70%-100% (n = 3588) n (%)	0%-69% (n = 3279) n (%)	*P*
Molecular subtype							.05
Luminal A	603 (8.1)	456 (8.6)	129 (6.6)		325 (9.1)	239 (7.3)	
Luminal B	3968 (53.4)	2817 (52.9)	1071 (54.6)		1985 (55.3)	1725 (52.6)	
HER2 positive	728 (9.8)	514 (9.7)	200 (10.2)		343 (9.6)	334 (10.2)	
Triple-negative	863 (11.6)	623 (11.7)	230 (11.7)		391 (10.9)	410 (12.5)	
Unknown	1274 (17.1)	917 (17.2)	332 (16.9)		544 (15.1)	571 (17.4)	
Tumor stage				.05			.05
I	1406 (18.9)	1107 (20.8)	271 (13.8)		753 (21.0)	572 (17.4)	
II	3182 (42.8)	2300 (43.2)	820 (41.8)		1565 (43.5)	1385 (42.2)	
III	1713 (23.1)	1147 (21.5)	531 (27.1)		791 (22.1)	771 (23.6)	
IV	180 (2.4)	119 (2.2)	56 (2.9)		89 (2.5)	90 (2.7)	
Unknown	955 (12.8)	654 (12.3)	284 (14.4)		390 (10.9)	461 (14.1)	
Histological type				.05			
Ductal	6897 (92.8)	4910 (92.2)	1849 (94.2)		3321 (92.6)	3076 (93.8)	
Others	308 (4.1)	228 (4.3)	75 (3.9)		158 (4.4)	125 (3.8)	
Unknown	231 (3.1)	189 (3.5)	38 (1.9)		109 (3.0)	78 (2.4)	
Histological grade				.05			.05
I	194 (2.6)	152 (2.9)	34 (1.7)		96 (2.7)	87 (2.7)	
II	2216 (29.8)	1628 (30.6)	549 (28.0)		1154 (32.2)	933 (28.4)	
III	3134 (42.2)	2212 (41.5)	868 (44.2)		1492 (41.5)	1412 (43.1)	
Unknown	1892 (25.4)	1335 (25.0)	511 (26.1)		846 (23.6)	847 (25.8)	

Note: Patients with missing information on insurance type (n = 147, 1.98%) or reimbursement rate (n = 569, 7.65%) were not included for the corresponding analysis. Body mass index (BMI) was classified into <23 kg/m^2 (non-overweight) and ≥23 kg/m^2 (overweight). Tumor stage was categorized as localized (no nodal or metastatic disease), regional (nodal disease), or distant (any metastatic disease). Pearson's χ^2 statistic was used to assess significance of the difference between proportions in assessment of univariable associations.
Abbreviation: HER2, human epidermal growth factor receptor 2.

3 | RESULTS

3.1 | Patients' characteristics

About 1962 (26.9% of 7289 patients with known insurance type) were insured by rural schemes, and 3279 (47.8% of 6867 patients with known reimbursement rate) were reimbursed ≤69% of their healthcare cost. Patients insured by rural schemes were younger and diagnosed more recently. They were less likely to be Han people, less well-educated, nonmarried and postmenopausal, as well as with lower BMI and fewer comorbidities at diagnosis (all $P < .05$; Table 1). Their tumors were more likely to be HER2-positive, highly proliferative (Ki-67 ≥ 14%), poorly differentiated, and to have an advanced stage and ductal origin. Similar patterns were found for patients with reimbursement rate ≤69%. Underinsured patients were less treated by radiotherapy, hormonal therapy and trastuzumab, independent of tumor characteristics and other types of treatment (Table 2). In addition, patients with low reimbursement rate were less likely to undergo surgery, whereas patients insured by rural schemes were more likely to receive chemotherapy.

3.2 | Health insurance and breast cancer-specific mortality

During follow-up (median 3.1 years, interquartile range 1.4-5.1 years), 372 deaths were observed and 326 of them were due to breast cancer. The cumulative rates of breast cancer-specific mortality were higher among patients insured within rural insurance schemes and with reimbursement rates ≤69%, compared to patients with urban insurance schemes and higher reimbursement rates, respectively (Figure 1). Similar patterns were noticed for overall mortality.

When adjusting for demographic characteristics, patients insured by rural insurance schemes had a 46% increased risk of cancer-specific mortality (95% CI 14%-87%) compared to patients within urban insurance schemes (Table 3). With additional control for clinical characteristics and

TABLE 2 Associations of insurance type and reimbursement rate with treatment type, by demographic and clinical characteristics

	Number of patients	Number of events	%	Model A[a]		Model B[b]		Model C[c]	
				OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Surgery									
By insurance type									
Urban schemes	5327	5130	96.3	1.00		1.00		1.00	
Rural schemes	1962	1846	94.1	0.65 (0.50-0.83)	.001	0.71 (0.54-0.92)	.015	0.85 (0.65-1.13)	.261
By reimbursement rate									
70%-100%	3588	3471	96.7	1.00		1.00		1.00	
0%-69%	3279	3116	95.0	0.62 (0.49-0.80)	<.001	0.67 (0.51-0.87)	.003	0.75 (0.57-0.98)	.038
Chemotherapy									
By insurance type									
Urban schemes	5327	4913	92.2	1.00		1.00		1.00	
Rural schemes	1962	1865	95.1	1.56 (1.22-1.98)	<.001	1.36 (1.04-1.78)	.010	1.40 (1.06-1.83)	.016
By reimbursement rate									
70%-100%	3588	3335	93.0	1.00		1.00		1.00	
0%-69%	3279	3091	94.3	1.16 (0.95-1.42)	.140	1.14 (0.91-1.42)	.263	1.15 (0.92-1.45)	.214
Radiotherapy									
By insurance type									
Urban schemes	5327	1694	31.8	1.00		1.00		1.00	
Rural schemes	1962	560	28.5	0.87 (0.77-0.98)	.048	0.72 (0.63-0.83)	<.001	0.77 (0.67-0.88)	<.001
By reimbursement rate									
70%-100%	3588	1193	33.3	1.00		1.00		1.00	
0%-69%	3279	984	30.0	0.84 (0.76-0.94)	.002	0.78 (0.69-0.88)	<.001	0.81 (0.72-0.91)	.001
Hormonal therapy									
By insurance type									
Urban schemes	5327	3546	66.6	1.00		1.00		1.00	
Rural schemes	1962	1154	58.8	0.71 (0.63-0.80)	<.001	0.62 (0.53-0.72)	<.001	0.67 (0.57-0.79)	<.001
By reimbursement rate									
70%-100%	3588	2464	68.7	1.00		1.00		1.00	
0%-69%	3279	2041	62.2	0.74 (0.67-0.82)	<.001	0.74 (0.63-0.86)	<.001	0.79 (0.68-0.93)	.004
Use of trastuzumab									
By insurance type									
Urban schemes	5327	523	9.8	1.00		1.00		1.00	
Rural schemes	1962	80	4.1	0.44 (0.34-0.56)	<.001	0.33 (0.25-0.43)	<.001	0.33 (0.28-0.49)	<.001
By reimbursement rate									
70%-100%	3588	374	10.4	1.00		1.00		1.00	
0%-69%	3279	221	6.7	0.70 (0.59-0.83)	<.001	0.57 (0.47-0.70)	<.001	0.68 (0.66-0.89)	.006

Note: Patients with missing information on insurance type (n = 147, 1.98%) or reimbursement rate (n = 569, 7.65%) were not included for the corresponding analysis.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]ORs were adjusted for age at diagnosis, calendar year at diagnosis (2009-2012 or 2013-2016), ethnic group (majority or minority/unknown), education (>6 years, or ≤6 years/unknown) and marital status (married or nonmarried).

[b]ORs were additionally adjusted for comorbidity (no or yes), hormone receptor status (negative, positive or unknown), HER2 status (negative, positive or unknown), Ki-67 level (<14%, ≥14% or unknown), histological type (ductal or other types/unknown) and tumor stage (I, II, III, IV or unknown).

[c]ORs were additionally adjusted for treatment types, whenever applicable, including surgery (yes or no), chemotherapy (yes or no), radiotherapy (yes or no), hormonal therapy (yes or no) or trastuzumab therapy (yes or no).

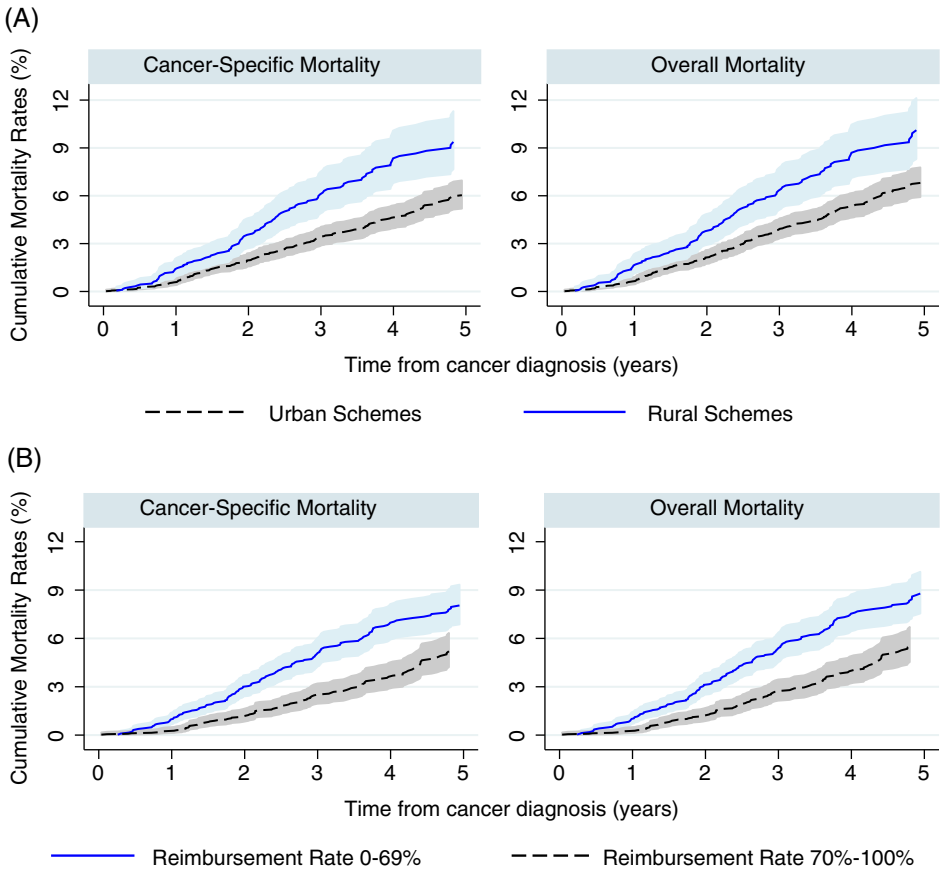

FIGURE 1 Cumulative mortality rates of cancer-specific or overall mortality by, A, insurance type and B, reimbursement rate. *Note:* Patients with missing information on insurances type (n = 147, 1.98%) were not included in the Analysis A. Patients with missing information on reimbursement rate (n = 569, 7.65%) were not included in Analysis B [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Associations of insurance type and reimbursement rate with risks of breast cancer-specific or overall mortality

	Number of patients	Number of events	Rate	Model A[a]		Model B[b]		Model C[c]	
				HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Breast cancer-specific mortality									
By insurance type									
Urban schemes	5327	211	1.16	1.00		1.00		1.00	
Rural schemes	1962	109	1.84	1.46 (1.14-1.87)	.003	1.32 (1.03-1.69)	.028	1.29 (1.00-1.65)	.046
By reimbursement rate									
70%-100%	3588	115	0.97	1.00		1.00		1.00	
0%-69%	3279	172	1.52	1.60 (1.25-2.04)	<.001	1.56 (1.22-1.99)	<.001	1.42 (1.11-1.2)	<.005
Overall mortality									
By insurance type									
Urban schemes	5327	248	1.37	1.00		1.00		1.00	
Rural schemes	1962	118	1.99	1.41 (1.11-1.78)	.004	1.30 (1.03-1.64)	.028	1.27 (1.01-1.61)	.045
By reimbursement rate									
70%-100%	3588	124	1.04	1.00		1.00		1.00	
0%-69%	3279	192	1.70	1.68 (1.33-2.12)	<.001	1.66 (1.32-2.10)	<.001	1.52 (1.20-1.93)	<.001

Note: Patients with missing information on insurance type (n = 147, 1.98%) or reimbursement rate (n = 569, 7.65%) were not included for the corresponding analysis.

Abbreviations: CI, confidence interval; HR, hazard ratio; Rate, mortality rate (per 100 person-years).

[a]HRs were adjusted for age at diagnosis, calendar year at diagnosis, ethnic group (majority or minority/unknown), education (>6 years, or ≤6 years/unknown) and marital status (married or nonmarried).

[b]HRs were additionally adjusted for comorbidity (no or yes), hormone receptor status (negative, positive or unknown), HER2 status (negative, positive or unknown), Ki-67 level (<14%, ≥14% or unknown), histological type (ductal or other types/unknown) and tumor stage (I, II, III, IV or unknown).

[c]HRs were additionally adjusted for surgery (yes or no), chemotherapy (yes or no), radiotherapy (yes or no), hormonal therapy (yes or no) and trastuzumab therapy (yes or no).

TABLE 4 Association of every 10% insurance reimbursement rate increase with risks of cancer-specific or overall mortality

	Number of patients	Number of events	Rate	Model A[a]		Model B[b]		Model C[c]	
				HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Breast cancer-specific mortality									
Any insurance type									
Per 10% increase	6867	287	1.33	0.90 (0.86-0.95)	<.001	0.91 (0.87-0.96)	0.001	0.93 (0.88-0.98)	.008
Within urban schemes									
Per 10% increase	4993	191	1.16	0.92 (0.84-1.00)	.078	0.91 (0.83-1.00)	0.052	0.94 (0.86-1.03)	.215
Within rural schemes									
Per 10% increase	1743	92	1.84	0.70 (0.58-0.84)	<.001	0.73 (0.60-0.89)	0.002	0.74 (0.61-0.91)	.004
P for difference[d]				0.007		0.039		0.039	
Overall mortality									
Any insurance type									
Per 10% increase	6867	316	1.52	0.90 (0.86-0.95)	<.001	0.91 (0.86-0.95)	<0.001	0.92 (0.88-0.97)	.002
Within urban schemes									
Per 10% increase	4993	214	1.37	0.89 (0.83-0.98)	.014	0.89 (0.82-0.97)	0.008	0.92 (0.84-1.00)	.051
Within rural schemes									
Per 10% increase	1743	98	1.99	0.72 (0.60-0.85)	<.001	0.75 (0.62-0.90)	0.002	0.76 (0.63-0.92)	.005
P for difference[d]				0.016		0.087		0.087	

Note: Patients with missing information on insurance type (n = 147, 1.98%) or reimbursement rate (n = 569, 7.65%) were not included for the corresponding analysis.

Abbreviations: CI, confidence interval; HR, hazard ratio; Rate, mortality rate (per 100 person-years).

[a]HRs were adjusted for age at diagnosis, calendar year at diagnosis, ethnic group (majority or minority/unknown), education (>6 years or ≤6 years/unknown) and marital status (married or nonmarried).

[b]HRs were additionally adjusted for comorbidity (no or yes), hormone receptor status (negative, positive or unknown), HER2 status (negative, positive or unknown), Ki-67 level (<14%, ≥14% or unknown), histological type (ductal or other types/unknown) and tumor stage (I, II, III, IV or unknown).

[c]HRs were additionally adjusted for surgery (yes or no), chemotherapy (yes or no), radiotherapy (yes or no), hormonal therapy (yes or no) and trastuzumab therapy (yes or no).

[d]We added an interaction term between insurance type and reimbursement rate (as continuous variable) in the model, and reported the *P* value of the interaction term as a significance test of the difference between HRs.

treatment modes, the association was attenuated somewhat yet remained significant (HR 1.29, 95% CI 1.00-1.65). Similarly, patients with low reimbursement rate had a 42% increased risk of cancer-specific mortality (95% CI 11%-82%) compared to patients within high reimbursement rate. Similar patterns were found for overall mortality (Table 3).

Largely similar results were yielded for both insurance type and reimbursement rate after additional control for BMI (Table S1). Comparable but less significant associations were observed by conditioning on residential areas to further address SES and accessibility to care (Table S2).

3.3 | Joint effect of insurance type and reimbursement rate

We showed that every 10% increase in the reimbursement rate was associated with a 7% reduced risk of cancer-specific mortality (95% CI 2%-12% after full adjustment; Table 4). Particularly, every 10% increase of reimbursement rate in rural insurance schemes was associated with remarkable risk reduction of cancer-specific mortality (HR 0.74, 95% CI 0.61-0.91), compared to that in urban insurance schemes (HR 0.94, 95% CI 0.86-1.03, *P* for difference = .039). Similar results were found in overall mortality (Table 4).

4 | DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that underinsured patients with invasive breast cancer are at increased risk of cancer-specific mortality in a country with less developed health insurance system. Importantly, our findings strongly suggest that a higher reimbursement rate, particularly in rural scheme insurance, is associated with a remarkable risk reduction of breast cancer-specific mortality. These associations are partly but not entirely explained by known prognostic indicators, including tumor characteristics and cancer treatment.

Findings from several studies in developed countries, mostly from the US, have shown that underinsured patients with breast cancer are more likely to suffer an increased risk of cancer-specific mortality, compared to those with adequate insurance.[10-13] Only one study from developing countries showed that breast cancer prognosis is comparable between patients insured by public and private health

insurances.[16] Our data further illustrated the impact of public health insurance status on breast cancer prognosis in developing countries independent of clinical factors. Most importantly, in addition to insurance status or type, we are the first to reveal that the low reimbursement rate is associated with an excess risk of breast cancer-specific mortality. In many developed countries, insurance plans usually come with a fixed coinsurance or reimbursement rate. Our setting therefore provides a unique opportunity to understand the potential mechanisms underlying the relationship between insurance and cancer prognosis, which highlights the urgent need of promoting reimbursement rate in rural insurance schemes, to significantly improve breast cancer prognosis and reduce health disparities at large.

Several mechanisms may contribute to the observed association of suboptimal health insurance and compromised prognosis after a breast cancer diagnosis. It is plausible that underinsured patients have limited access to medical service, which may lead to delayed diagnosis and suboptimal treatment.[19] This is also supported by our data that patients insured by rural schemes or with low reimbursement rate were more likely to have an advanced tumor stage and were less treated by radiotherapy, hormonal therapy and trastuzumab, independent of tumor characteristics and other types of treatment. In general, primary care is less established in rural areas, and no organized screening program for breast cancer is in place in Sichuan, which may result in delayed cancer diagnosis among rural living women.[19,23] Indeed, our analysis showed that the associations between inadequate insurance and breast cancer-specific mortality attenuated to some extent after adjusting for tumor characteristics, suggesting the mediating role of more advanced tumor stage. Moreover, underinsured patients face greater financial burden and are less likely to afford out-of-pocket medical expenses for advanced therapy.[24] For instance, trastuzumab was not covered by the insurances during the study period, and the high out-of-pocket medical cost may prevent financially vulnerable patients from such therapy. In line with that, our data indicated a further attenuated association after controlling for cancer treatment, in support of the contribution of limited cancer care.

However, the increased risk of mortality among underinsured patients with breast cancer is not entirely explained by the differential tumor characteristics and treatment modes. In the present study, the elevated risks of cancer-specific mortality remained robust, although slightly attenuated, among patients insured by rural insurance schemes or with low reimbursement rate, after exhaustive adjustment for clinical factors. It is known that cancer diagnosis and treatment induce enormous psychological stress in cancer patients.[25] The financial hardship, as a result of inadequate insurance, may add extra emotional turmoil to cancer patients. A growing body of evidence from animal studies suggests that psychological stress might modulate cancer progression through facilitating tumor growth and invasion as well as inhibiting host immune responses, operated by the hypothalamic-pituitary-adrenal axis.[26] It is not implausible that the lack of financial support may impact breast cancer prognosis through psychological stress.

Our findings may partly reflect the difference of SES across rural and urban regions as well as between individuals. Of note, SES is highly correlated with, and to some extent reflected by, health insurance status. As health insurance is likely underlying the causal pathway between SES and cancer prognosis, we did not consider it as a confounder in the studied association. However, we have adequately addressed educational attainment (as a proxy for SES) in all analyses. To further separate the influence of SES, we performed a sensitivity analysis by conditioning on 88 residence areas to better control for SES and accessibility to healthcare. Increased risks of cancer-specific and overall mortality are still suggested, although some are not significantly likely due to power issues. This largely refutes the possibility that our findings are completely explained by the differential socioeconomic status.

One major merit of our study is the large-scale prospective cohort design with virtually complete follow-up, largely limiting the common sources of bias. The rich information on demographic and clinical characteristics helped to disentangle the direct influence of health insurance on cancer-specific mortality, from the influence through tumor characteristics and treatment modes. Our study also has several limitations to consider. First, some deaths due to other causes may be misclassified as breast cancer-specific mortality. However, in our data, 297 out of 326 cancer-specific deaths (91.1%) entailed a clinically detected local recurrence or distant metastasis, which largely alleviates such concerns. Moreover, the 5-year breast cancer-specific survival rate in our cohort is comparable to other Chinese cohorts[27,28] and cohorts from developed countries,[6,29] given a similar distribution of tumor stage. Furthermore, we have little information regarding extra insurances beyond the basic/public insurance. However, there were only 11 patients with commercial insurances included in our study and it is less likely to impact our results. As this cohort is based on a regional medical center, the findings may not be generalized to the entire population. The major selection forces include urban and well-educated residents, as well as advanced disease yet eligible for surgery and chemotherapy/radiotherapy due to referrals from other hospitals. We, however, observed similar associations across regions of residence, educational levels, and tumor stages (data not shown). We may also miss the patients that are most financially vulnerable, because of the nature of our study setting. Reassuringly, we noted the strongest association in the youngest patients (aged 18-39 years), where we should have a smaller selection force because young patients with breast cancer were more likely to seek healthcare in a tertiary hospital.

In conclusion, our findings suggest that underinsured patients face a higher risk of breast cancer-specific mortality in China, which may provide fresh insights into the role of reimbursement rate in cancer health disparities in China and likewise developing countries.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data and other items supporting the results in the paper will be made available upon reasonable request to the corresponding authors.

ETHICS STATEMENT

Our study is approved by the Clinical Test and Biomedical Ethics Committee at West China Hospital, Sichuan University (reference number 2012-130). Consent forms have been obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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