

Cardiorenal outcomes following herpes zoster reactivation in COVID-19 survivors: a global multicenter study using TriNetX

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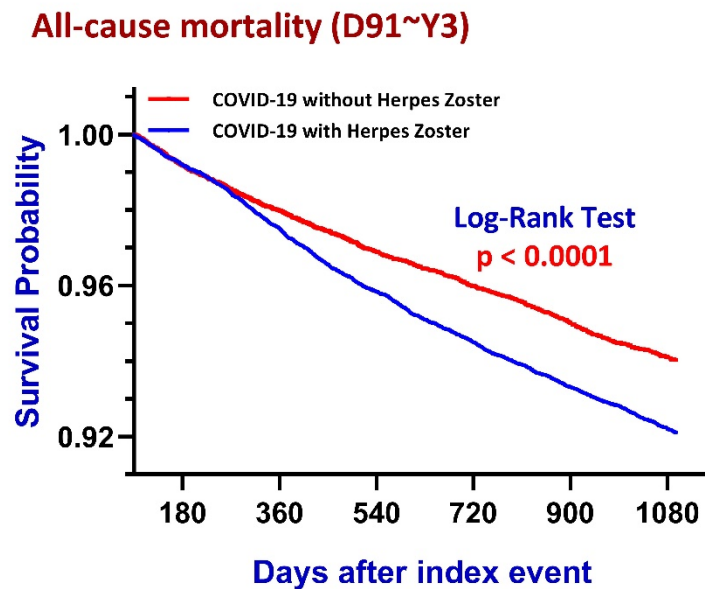
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Supplementary Figure S1. Kaplan–Meier survival analysis of all-cause mortality from day 91 to 3 years after COVID-19 diagnosis, stratified by herpes zoster (HZ) status.



In the HZ group ($n = 27,125$), 1,943 deaths occurred (7.2% risk), while 1,147 deaths were recorded in the non-HZ group ($n = 26,864$), corresponding to a 4.3% risk. The estimated risk difference was 2.9% (95% CI: 2.5–3.3%; $p < 0.001$). The three-year survival probabilities were 92.1% for the HZ group and 94.0% for the non-HZ group. The log-rank test indicated a statistically significant difference between groups ($\chi^2 = 60.322$, $p < 0.001$). The HR for mortality was 1.33 (95% CI: 1.24–1.44), and the proportional hazards assumption was satisfied (proportionality test $p = 0.897$).

Supplementary Table S1. Time-stratified hazard ratios for all-cause mortality over a 1-year follow-up in COVID-19 patients with and without herpes zoster (HZ).

All-cause mortality	Cohorts	Hazard ratio	95% CI	Log-Rank Test
1-90 days	Patients with HZ Patients without HZ	0.30	(0.25, 0.36)	$p < 0.001$
91-180 days	Patients with HZ Patients without HZ	1.16	(0.92, 1.45)	$p = 0.210$
181-270 days	Patients with HZ Patients without HZ	1.45	(1.13, 1.87)	$p < 0.005$
271-360 days	Patients with HZ Patients without HZ	1.55	(1.24, 1.94)	$p < 0.001$

Supplementary Table S2. Incidence of healthcare utilization during 1-year follow-up among COVID-19 patients with and without herpes zoster (HZ).

Incident visits	Cohorts	Number of visits (mean)	Number of visits (SD)	<i>p</i> value
1-90 days	Patients with HZ	4.171	8.072	<i>p</i> < 0.001
	Patients without HZ	2.358	5.457	
91-180 days	Patients with HZ	3.374	6.971	<i>p</i> < 0.001
	Patients without HZ	1.522	4.345	
181-270 days	Patients with HZ	3.004	6.492	<i>p</i> < 0.001
	Patients without HZ	1.316	3.944	
271-360 days	Patients with HZ	3.094	6.681	<i>p</i> < 0.001
	Patients without HZ	1.299	3.941	

Supplementary Table S3. Sensitivity analysis excluding patients with chronic kidney disease (CKD) within 1 year prior to COVID-19 diagnosis.

Outcomes	Patients with HZ (n/N)	Patients without HZ (n/N)	HR (95% CI)	<i>p</i> value
All-cause mortality	844/18,426	642/18,447	1.03 (0.93–1.14)	0.608
MACE	2013/14,168	1311/15,640	1.35 (1.26–1.45)	< 0.001
AKI	866/17,925	461/18,179	1.496 (1.34–1.68)	< 0.001
eGFR <60	1548/16,797	1016/17,424	1.232 (1.14–1.33)	< 0.001

Abbreviation: AKI, acute kidney injury; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HZ, herpes zoster; MACE, major adverse cardiovascular events; n/N, number of events/total number of patients.

Supplementary Table S4. Sensitivity analysis excluding patients with acute kidney injury (AKI) within 1 year prior to COVID-19 diagnosis.

Outcomes	Patients with HZ (n/N)	Patients without HZ (n/N)	HR (95% CI)	<i>p</i> value
All-cause mortality	1200/21126	914/21163	1.04 (0.96–1.13)	0.361
MACE	2423/15407	1702/17214	1.28 (1.20–1.36)	< 0.001
AKI	1170/20365	649/20821	1.46 (1.33–1.61)	< 0.001
eGFR <60	1794/17184	1218/18422	1.256 (1.17–1.35)	< 0.001

Abbreviation: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HZ, herpes zoster; MACE, major adverse cardiovascular events; n/N, number of events/total number of patients.

Supplementary Table S5. Sensitivity analysis excluding patients with influenza within 1 year before or after COVID-19 diagnosis.

Outcomes	Patients with HZ (n/N)	Patients without HZ (n/N)	HR (95% CI)	<i>p</i> value
All-cause mortality	1893/23,365	1521/23,347	0.99 (0.93–1.06)	0.772
MACE	2,841/16,136	1845/18,334	1.42 (1.34–1.51)	< 0.001
AKI	1959/20,848	989/21,754	1.70 (1.57–1.83)	< 0.001
eGFR <60	2119/17,725	1468/19,442	1.27 (1.19–1.36)	< 0.001

Abbreviation: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HZ, herpes zoster; MACE, major adverse cardiovascular events; n/N, number of events/total number of patients.

Supplementary Table S6. Sensitivity analysis in the overall COVID-19 cohort with adjustment for age, sex, race, and comorbidities.

Outcomes	Patients with HZ (n/N)	Patients without HZ (n/N)	HR (95% CI)	<i>p</i> value
All-cause mortality	1936 /24,211	1621/24,198	0.98 (0.919–1.044)	0.520
MACE	3198/18,040	2217/19,632	1.31 (1.238–1.380)	< 0.001
AKI	2161/23,419	1312/24,135	1.44 (1.342–1.539)	< 0.001
eGFR <60	2429/19,839	1720/21,144	1.25 (1.172–1.326)	< 0.001

Abbreviation: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HZ, herpes zoster; MACE, major adverse cardiovascular events; n/N, number of events/total number of patients.

Supplementary Table S7. Sensitivity analysis in the overall COVID-19 cohort with adjustment for age, sex, race, comorbidities, and laboratory parameters.

Outcomes	Patients with HZ (n/N)	Patients without HZ (n/N)	HR (95% CI)	<i>p</i> value
All-cause mortality	1936 /24,211	1621/24,198	0.968 (0.908–1.031)	0.310
MACE	3198/18,040	2217/19,632	1.298 (1.229–1.370)	< 0.001
AKI	2161/23,419	1312/24,135	1.396 (1.304–1.494)	< 0.001
eGFR <60	2429/19,839	1720/21,144	1.228 (1.154–1.305)	< 0.001

Abbreviation: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HZ, herpes zoster; MACE, major adverse cardiovascular events; n/N, number of events/total number of patients.

Supplementary Table S8. Sensitivity analysis of 1–90-day all-cause mortality among patients with and without post-COVID herpes zoster (HZ), excluding individuals with prior chronic kidney disease (CKD) or acute kidney injury (AKI).

Time window	CKD/AKI Exclusion	Cohort	Hazard ratio	95% CI	<i>p</i> value
1-90 days	No	Patients with HZ	0.30	(0.25, 0.36)	<i>p</i> < 0.001
		Patients without HZ	Reference		
1-90 days	Yes	Patients with HZ	0.36	(0.29, 0.45)	<i>p</i> < 0.001
		Patients without HZ	Reference		

Abbreviations: HZ, herpes zoster; CKD, chronic kidney disease; AKI, acute kidney injury.

Supplementary Table S9. Sensitivity analysis of all-cause mortality and cardiorenal outcomes stratified by COVID-19 vaccination status.

Vaccination status	Outcome	HR	95% CI	<i>p</i> value
With vaccination	All-cause mortality	1.25	(1.06, 1.47)	<i>p</i> < 0.05
	MACE	1.36	(1.21, 1.52)	<i>p</i> < 0.05
	AKI	1.38	(1.20, 1.60)	<i>p</i> = 0.07
	eGFR < 60 mL/min/1.73 m ²	1.29	(1.14, 1.46)	<i>p</i> = 0.08
Without vaccination	All-cause mortality	1.05	(0.98, 1.12)	<i>p</i> < 0.001
	MACE	1.29	(1.22, 1.37)	<i>p</i> < 0.001
	AKI	1.65	(1.53, 1.77)	<i>p</i> < 0.001
	eGFR < 60 mL/min/1.73 m ²	1.20	(1.13, 1.28)	<i>p</i> < 0.05

Abbreviations: HZ, herpes zoster; MACE, major adverse cardiovascular events; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

Supplementary Table S10. Distribution of age at index and current age before and after propensity score matching.

Demographics		Before matching			After matching		
		Mean ± SD	Patients	Std diff.	Mean ± SD	Patients	Std diff.
Age at Index	Patients	58.3					
	with	±	29,088		58.3 ± 15.6	29,088	
	HZ	15.6		0.588			< 0.001
	Patients	48.3					
	without	±	10,312,206		58.3 ± 15.6	29,088	
	HZ	18.1					
Current Age	Patients	62.8					
	with	±	29,088		62.8 ± 15.6	29,088	
	HZ	15.6		0.589			< 0.001
	Patients	52.8			62.8 ± 15.6	29,088	
	without	±	10,312,206				
	HZ	18.2					

Abbreviations: HZ, herpes zoster; Std diff., standardized difference.

Supplementary Table S11. Incidence and frequency of COVID-19 reinfection in patients with and without post-COVID herpes zoster (HZ).

Cohort	Patients in cohort	Patients with outcome	Risk (%)	Mean reinfection instances	Standard deviation	<i>p</i> value
Patients with HZ	29,088	20,668	0.71	2.895	5.13	p < 0.001
Patients without HZ	29,088	15,486	0.53	1.662	3.646	