

Psoriasis-related treatment exposure and hospitalization or in-hospital mortality due to COVID-19 during the first and second wave of the pandemic: cohort study of 1 326 312 patients in France*

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Summary

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Conflicts of interest

No conflict of interest for the co-authors.

Data availability statement

We used the French national health data system [Système National des Données de Santé (SNDS)], which covers the entire French population (i.e. 67 million inhabitants in France).

M.Z. and E.S. contributed equally to the study.

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Background Data on treatment exposures for psoriasis and poor COVID-19 outcomes are limited.

Objectives To assess the risk of hospitalization or in-hospital mortality due to COVID-19 by treatment exposure in patients with psoriasis.

Methods All adults with psoriasis registered in the French national health-insurance (Système National des Données de Santé, SNDS) database between 2008 and 2019 were eligible. Two study periods were considered: 15 February to 30 June 2020 and 1 October 2020 to 31 January 2021, the first and second waves of the COVID-19 pandemic in France, respectively. Patients were classified according to their baseline treatment: biologics, nonbiologics, topicals or no treatment. The primary endpoint was hospitalization for COVID-19 using Cox models with inverse probability of treatment weighting. The secondary endpoint was in-hospital mortality due to COVID-19.

Results We identified 1 326 312 patients with psoriasis (mean age 59 years; males, 48%). During the first study period, 3871 patients were hospitalized for COVID-19 and 759 (20%) died; during the second period 3603 were hospitalized for COVID-19 and 686 (19%) died. In the propensity score-weighted Cox models, risk of hospitalization for COVID-19 was associated with exposure to topicals or nonbiologics [hazard ratio (95% confidence interval): 1.11 (1.04–1.20) and 1.27 (1.09–1.48), respectively] during the first period, and with all exposure types, during the second period. None of the exposure types was associated with in-hospital mortality due to COVID-19.

Conclusions Systemic treatments for psoriasis (including biologics) were not associated with increased risk of in-hospital mortality due to COVID-19. These results support maintaining systemic treatment for psoriasis during the pandemic.

What is already known about this topic?

- Almost all chronic diseases have emerged as risk factors for hospitalization for COVID-19 and poor COVID-19 outcomes.
- Multimorbidity is frequent in psoriasis. In France, psoriasis was found to be associated with increased risk of hospitalization for COVID-19 but not in-hospital mortality due to COVID-19.

- Biologics are associated with an increased risk of infection. Few data have been published on the course of COVID-19 in patients with psoriasis receiving biologics.

What does this study add?

- Systemic treatments for psoriasis (including nonbiologics and biologics) were not associated with an increased risk of in-hospital mortality due to COVID-19.
- Our results did not support a prophylactic effect of long-term use of biologics on risk of hospitalization for COVID-19 or in-hospital mortality.
- These results provide evidence supporting the continuity of care for psoriasis and maintaining systemic treatment for psoriasis during the pandemic.

During the COVID-19 pandemic, more than 150 million people around the world have been infected with SARS-CoV-2, with more than 3 million deaths as of 1 May 2021. By the same date, in France, 5.5 million patients had tested positive for the virus and 100 000 had died.^{1,2}

Large cohort studies have identified prognostic factors of infection such as age, male sex and chronic diseases. In the UK, a study by Williamson *et al.*, assessing more than 17 million individuals, showed increased risk of COVID-19-related death with autoimmune diseases, defined as rheumatoid arthritis, lupus or psoriasis (a total of 878 475 individuals).³ Assessing 67 million inhabitants in France, psoriasis was found to be associated with increased risk of hospitalization for COVID-19 but not in-hospital mortality due to COVID-19 [adjusted hazard ratio (aHR) 1.13, 95% confidence interval (CI) 1.04–1.23 and 1.02, 0.81–1.29, respectively]. These results were adjusted for age, sex, location of residence, and more than 45 chronic disorders including obesity, diabetes, hypertension, heart diseases – factors that are associated with both severity of psoriasis^{4,5} and severity of COVID-19.⁶

Nonbiologic therapies, target therapies or biologics are used to manage moderate-to-severe psoriasis.⁷ Post-marketing studies have allowed for better understanding of their safety profile, demonstrating a favourable risk–benefit ratio despite increased risk of infection.⁸ In the current pandemic context, few data have been published on the course of COVID-19 in patients with psoriasis receiving biologic therapy.^{9–17} All experts agree that in the absence of infection, discontinuing biologic therapy is not recommended,^{18,19} a resurgence of the underlying pathology being potentially more deleterious than COVID-19. There is no evidence of increased risk of SARS-CoV-2 infection in immunocompromised patients.

Mahil *et al.* investigated factors associated with hospitalization for COVID-19 in patients with psoriasis. Clinicians from an international collaboration (25 countries, PsoProtect) reported 374 patients with psoriasis and confirmed or suspected COVID-19: 267 (71%) were using biologics and 67 (18%) nonbiologic systemic treatment; nine (2%) deaths were reported. In these preliminary results, hospitalization was

more frequent with nonbiologic systemic therapy than biologics (odds ratio 2.84, 95% CI 1.31–6.18). However, the number of patients involved was low and mortality could not be assessed.¹⁷ Despite the preliminary reassuring data, we observed a marked decrease of up to 60% in initiation of biologics for psoriasis during the first lockdown for COVID-19 in France (from March to May 2020), which was not compensated for during the following months.²⁰

To ensure continuity of care for psoriasis, this study aimed to provide data assessing the risk of hospitalization or in-hospital mortality due to COVID-19 by treatment exposure in patients with psoriasis, taking into account modifications of medical care over time.

Patients and methods

Setting and data sources

This was a retrospective nationwide cohort study in France using information from the French national health data system (Système National des Données de Santé, SNDS). The SNDS covers the entire French population (i.e. 67 million inhabitants in France). In the SNDS database, since 2006, an anonymous unique individual identifier has linked information from two principal data sources: the national health insurance claims database (DCIR) and the national hospital and discharge database (PMSI).^{21,22} The DCIR contains exhaustive data on all reimbursements for health-related expenditures, outpatient medical care and nursing care prescribed or performed by healthcare professionals. Although the SNDS does not specify the medical indication for all outpatient reimbursements, the health expenditure of patients with long-term diseases such as diabetes is fully reimbursed, and their diagnosis is recorded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The PMSI database provides detailed medical information on all admissions to French public- and private-sector hospitals, including the dates of hospital admission and discharge and the ICD-10 code on discharge.

Study population and follow-up procedures

All adults (≥ 18 years old) with psoriasis from 2008 to 2019 were eligible. Adults with psoriasis were defined as those who filled at least two prescriptions for topical formulations of vitamin D (Anatomical Therapeutic Chemical code D05AX, the recommended first-line treatment for psoriasis in France) within a 2-year period.^{23–25} Patients with HIV infection, organ transplantation or dialysis were excluded, as were patients who died before the study entry. Finally, we included all individuals who had received at least one reimbursement for healthcare within the 12-month period preceding the study entry (i.e. healthcare consumers).

We considered two different study periods, for two different entry dates (or index date), corresponding to:

- the first wave of the pandemic in France from 15 February 2020 (index date) to 15 June 2020. The end of follow-up was 15 July 2020.
- the second wave of the pandemic in France from 1 October 2020 (index date) to 31 December 2020. The end of follow-up was 31 January 2021.

We considered two different study periods, as the situation during the first and second wave was different in France (see

Figure 1). Indeed, national studies based on the health assurance database observed difficulties in accessing healthcare including several reasons: shutdown of medical facility, fear of contamination, rescheduling or cancelling of patients' medical appointments and fear of overcrowding the hospitals.²⁶ We also observed a decrease in the use of treatment for chronic diseases during the first lockdown. After lockdown, dispensing of treatment for chronic disease gradually returned to expected numbers.²⁷ Change in treatment advice was also observed with a decrease of up to 57% in the initiation of biologics for psoriasis healthcare users during the first lockdown.²⁰ Thus patients' risk-mitigating behaviours may have changed during the second part of the pandemic with a wider exposure to COVID-19.

Exposure definition

Patients were classified according to their exposure to treatments within the 6-month period before the index date: (i) biologics (at least one reimbursement of etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukizumab, ixekizumab, brodalumab, guselkumab); (ii) nonbiologics (at least one reimbursement of apremilast, methotrexate, ciclosporin, acitretin or phototherapy without any dispensation of

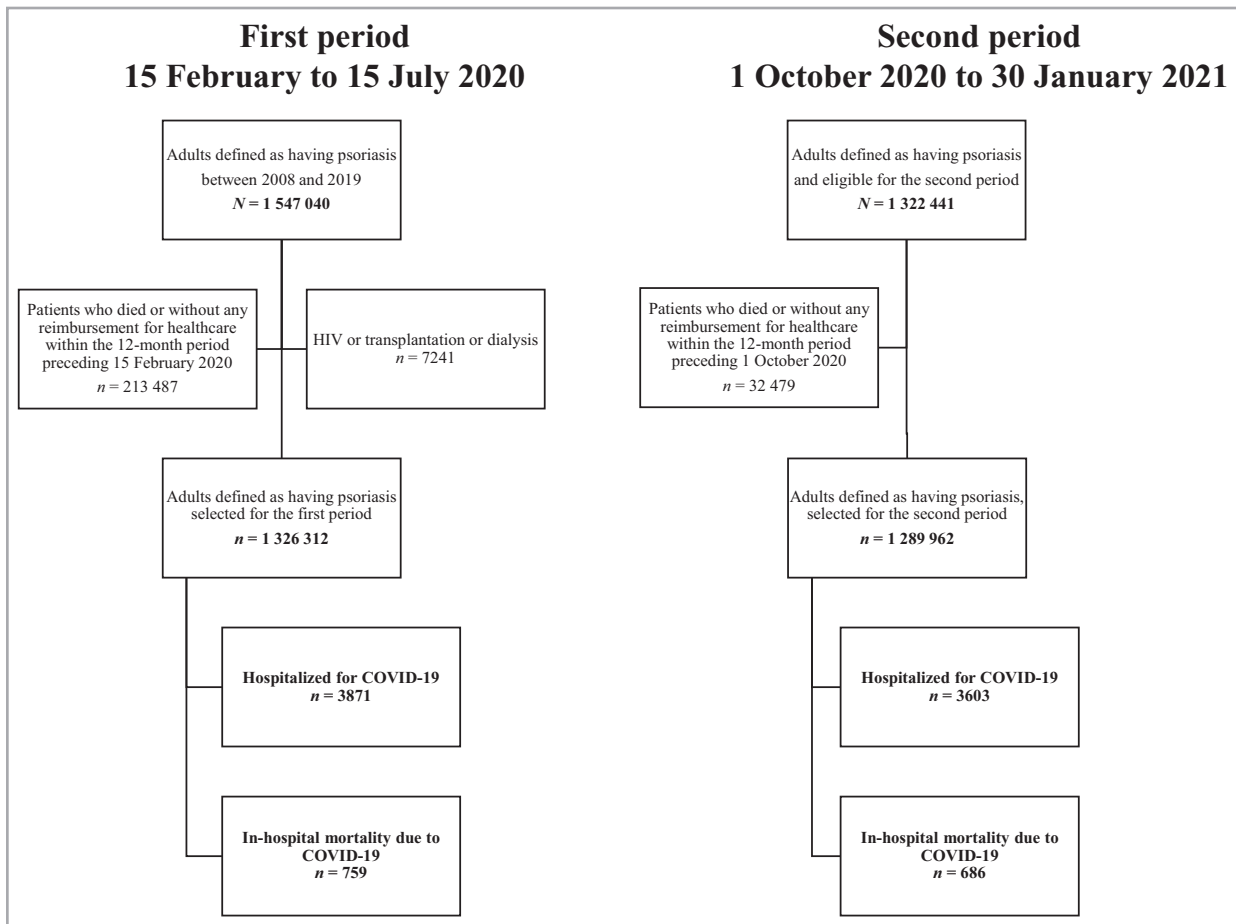


Figure 1 Flowchart of patients.

biologics); (iii) topical treatments (at least one reimbursement of corticosteroids and vitamin D derivative without any dispensation of systemic treatment); or (iv) none. Drugs were identified by using the Anatomical Therapeutic Chemical codes (Table S1, see Supporting Information). Risankizumab was marketed in France in January 2020 and was not assessed in this study.

Outcome

The primary endpoint was hospitalization for COVID-19. The secondary outcome was in-hospital mortality due to COVID-19. Diagnostic codes for COVID-19 are included in Table S1.

Covariates

For each patient, the following data were recorded for the 5-year period before the index date: age, sex, location of residence, deprivation index,^{3,28} comorbidities (metabolic disorders including diabetes and obesity; major adverse cardiovascular events including stroke, myocardial infarction and obliterating arteritis of the lower limbs; hypertension; chronic obstructive pulmonary disease; hepatic disease; cancer; psychological disorders; neurological disorders) and associated inflammatory diseases (rheumatoid arthritis and related disorders; ankylosing spondylitis and related disorders; inflammatory bowel disease). Details are in Table S1.

Statistical methods

Quantitative variables are reported as mean (SD) and categorical variables with number (percentage). Participants were followed until the occurrence of the main event (hospitalization or in-hospital mortality due to COVID-19) or the censorship date: death from any cause (date of death) or the study period date (as previously defined), whichever came first.

We compared outcomes for patients with and without exposure to psoriasis treatments (topical treatments, nonbiological systemic treatments and biologics) by using multivariable propensity score-weighted Cox models.

Using the Kaplan–Meier method, we calculated the crude hospitalization rates for COVID-19 by treatment exposure (no treatment was the reference). Risk differences were also computed. Then the aHR and its 95% CI was estimated by a cause-specific conditional Cox proportional hazards regression model to account for the competing risk between all-cause out-of-hospital death and hospitalizations for COVID-19. The proportional hazard assumption was tested by using Schoenfeld residuals. Finally, to help account for the nonrandomized treatment exposures, we used propensity-score methods to reduce the effects of confounding. The propensity score was estimated by using a multinomial logistic regression model that included all patient characteristics at baseline: age, sex, comorbidities (major adverse cardiovascular events, hypertension, metabolic diseases, chronic obstructive pulmonary disease, hepatic diseases, cancers and neurological illnesses). The

inverse probability of treatment weighting (IPTW) method was used to reduce potential bias due to treatment allocation. Weights were based on the propensity score. Because the treatment groups were of unequal size, the IPTW was stabilized by multiplying the IPTW by the marginal probability of receiving each treatment to preserve the sample size of the original data and produce an appropriate estimate of the main effect variance. IPTW weights were not truncated. We assessed time to hospitalization for COVID-19 by using IPTW analyses with cause-specific Cox models. The standardized difference of the mean was computed before and after IPTW to assess imbalance of the covariates between treatment groups. Standardized differences < 0.10 were considered negligible following common practice when using IPTW to estimate causal treatment effects in observational studies.^{29,30} Confounding variables that could not be balanced by the IPTW were added as adjustment variables. The same methodology was used for the secondary outcome (in-hospital mortality due to COVID-19). To better assess the risk of exposures for psoriasis on COVID-19 infection, we conducted subgroup analyses on patients with psoriasis without any comorbidities (major adverse cardiovascular events, hypertension, metabolic diseases, chronic obstructive pulmonary disease, hepatic diseases, cancers and neurological illnesses).

We also conducted several sensitivity analyses to check the stability of our results under varying approaches. Firstly, Fine–Gray competing risks analyses were performed, computing sub-HRs and 95% CIs. Then, we used a conventional multivariate Cox model to estimate aHRs and 95% CIs. Finally, treatment exposure was assessed within a 3-month and 9-month period before the index date.

All tests were bilateral. All analyses were performed with SAS Enterprise Guide v7.1 (SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance was set to $P < 0.05$.

Results

During the first study period, a total of 1 326 312 patients with psoriasis were identified [mean age 58.8 (16.4) years; males 48.4%; Figure S1 (see Supporting Information) and Table 1]. Overall, 321 837 (24.3%) were exposed to topical treatments: 49 459 (3.7%) to nonbiologics and 31 998 (2.4%) to biologics; 923 018 (69.6%) were not exposed within the 6-month period preceding the index date. During the second period, 1 289 962 patients with psoriasis were still eligible [mean age 59.3 (16.3) years; men 48.0%]. The proportion of systemic treatment exposure within the 6-month period preceding the second index date was similar to the first study period. More patients belonged to the unexposed group during the second vs. the first period (77% vs. 70%).

Patient characteristics are summarized in Table 1. In the two study periods, patients exposed to biologics were younger and had fewer comorbidities than the other treatment groups, except for inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis- and ankylosing spondylitis-related diseases) and hepatic diseases, which were more frequent.

Table 1 Characteristics of the study population with psoriasis by study period and treatment exposure^a

	First period (February to July 2020)				Second period (October 2020 to January 2021)					
	Unexposed	Topicals	Nonbiologics	Biologics	Total	Unexposed	Topicals	Nonbiologics	Biologics	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sociodemographic characteristics										
Age, mean (SD) years	58.9 (16.7)	59.2 (15.9)	58.9 (14.6)	52.3 (13.4)	58.8 (16.4)	59.4 (16.5)	60.1 (15.7)	59.4 (14.4)	52.6 (13.4)	59.3 (16.3)
Males	435 872 (47.2)	161 344 (50.1)	27 367 (55.3)	17 776 (55.6)	642 359 (48.4)	461 635 (46.3)	115 685 (53.3)	24 702 (54.7)	17 389 (55.1)	619 411 (48)
Associated inflammatory diseases and related disorders										
Rheumatoid arthritis	3156 (0.3)	2614 (0.8)	3157 (6.4)	1895 (5.9)	10 822 (0.8)	3702 (0.4)	2113 (1)	3005 (6.7)	1757 (5.6)	10 577 (0.8)
Psoriatic arthritis	711 (0.1)	597 (0.2)	1009 (2)	2679 (8.4)	4996 (0.4)	883 (0.1)	473 (0.2)	900 (2)	2513 (8)	4769 (0.4)
Ankylosing spondylitis	5780 (0.6)	3240 (1)	2765 (5.6)	6223 (19.4)	18 008 (1.4)	6842 (0.7)	2530 (1.2)	2688 (6)	6044 (19.1)	18 104 (1.4)
Inflammatory bowel disease	6036 (0.7)	2822 (0.9)	464 (0.9)	3775 (11.8)	13 097 (1)	6764 (0.7)	1975 (0.9)	420 (0.9)	3702 (11.7)	12 861 (1)
Comorbidities										
Major cardiovascular events	84 079 (9.1)	30 720 (9.6)	4383 (8.9)	2003 (6.3)	121 185 (9.1)	89 376 (9)	21 597 (10)	4067 (9)	1984 (6.3)	117 024 (9.1)
Stroke	24 821 (2.7)	7990 (2.5)	1074 (2.2)	449 (1.4)	34 334 (2.6)	25 646 (2.6)	5544 (2.6)	982 (2.2)	443 (1.4)	32 615 (2.5)
Coronary disease	63 637 (6.9)	24 148 (7.5)	3486 (7.0)	1623 (5.1)	92 894 (7)	67 967 (6.8)	17 037 (7.9)	3247 (7.2)	1616 (5.1)	89 867 (7)
Hypertension	337 353 (36.6)	126 481 (39.3)	18 566 (37.5)	9434 (29.5)	491 834 (37.1)	364 333 (36.6)	89 304 (41.2)	17 245 (38.2)	9363 (29.7)	480 245 (37.2)
Chronic obstructive pulmonary disease	76 654 (8.3)	48 024 (14.9)	4993 (10.1)	2812 (8.8)	132 483 (10)	83 983 (8.4)	28 737 (13.2)	4153 (9.2)	2459 (7.8)	119 332 (9.3)
Hepatic diseases	12 812 (1.4)	4920 (1.5)	887 (1.8)	1009 (3.2)	19 628 (1.5)	13 002 (1.3)	3510 (1.6)	756 (1.7)	876 (2.8)	18 144 (1.4)
Metabolic diseases	148 832 (16.1)	50 610 (15.7)	8359 (16.9)	5004 (15.6)	212 805 (16.0)	157 545 (15.8)	35 727 (16.5)	7577 (16.8)	4823 (15.3)	205 672 (15.9)
Diabetes	130 794 (14.2)	43 342 (13.5)	7209 (14.6)	3895 (12.2)	185 240 (14)	141 550 (14.2)	32 175 (14.8)	6747 (14.9)	3926 (12.4)	184 398 (14.3)
Obesity	25 769 (2.8)	10 009 (3.1)	1583 (3.2)	1509 (4.7)	38 870 (2.9)	21 368 (2.1)	4699 (2.2)	1116 (2.5)	1172 (3.7)	28 355 (2.2)
Cancer	31 675 (3.4)	14 694 (4.6)	2167 (4.4)	451 (1.4)	48 987 (3.7)	31 301 (3.1)	10 377 (4.8)	1798 (4)	414 (1.3)	43 890 (3.4)
Psychological illnesses	129 228 (14)	48 638 (15.1)	7026 (14.2)	4886 (15.3)	189 778 (14.3)	136 427 (13.7)	31 641 (14.6)	6270 (13.9)	4532 (14.4)	178 870 (13.9)
Neurological illnesses	37 312 (4)	10 371 (3.2)	1355 (2.7)	597 (1.9)	49 635 (3.7)	42 092 (4.2)	7821 (3.6)	1363 (3)	627 (2)	51 903 (4)
Treatments in the previous 2 years										
Biologics	2353 (0.3)	1370 (0.4)	962 (2)	29 336 (91.7)	34 021 (2.6)	3933 (0.4)	1456 (0.7)	946 (2.1)	29 688 (94)	36 023 (2.8)
Nonbiologics (without apremilast)	12 827 (1.4)	8582 (2.7)	35 892 (72.6)	10 477 (32.7)	67 778 (5.1)	14 695 (1.5)	6893 (3.2)	34 057 (75.4)	9572 (30.3)	65 217 (5.1)
Apremilast	1316 (0.1)	1271 (0.4)	6745 (13.6)	1254 (3.9)	10 586 (0.8)	3419 (0.3)	2154 (1)	7684 (17)	2069 (6.6)	15 326 (1.2)
Topicals	483 085 (52.3)	271 500 (84.4)	41 664 (84.2)	24 004 (75.0)	820 253 (61.8)	510 139 (51.2)	187 756 (86.5)	37 760 (83.6)	23 265 (73.7)	758 920 (58.8)
None of the above treatments	436 326 (47.3)	49 708 (15.4)	1214 (2.5)	214 (0.7)	487 462 (36.8)	481 161 (48.3)	28 735 (13.2)	794 (1.8)	154 (0.5)	510 844 (39.6)

^aData are n (%) unless otherwise indicated.

Risk of hospitalization or in-hospital mortality due to COVID-19

First study period

From 15 February to 15 June 2020, a total of 3871 patients met the primary endpoint and were hospitalized for COVID-19: 1025 (26.5%) with topical treatments, 171 (4.4%) nonbiologics, 73 (1.9%) biologics and 2602 (67.2%) unexposed. A total of 759 (20%) patients died from COVID-19: 203 (26.8%) with topical treatments, 25 (3.3%) nonbiologics, 4 (0.5%) biologics and 527 (69.4%) unexposed. Mean time to hospitalization for COVID-19 was 1.7 ± 0.6 months.

In the crude unadjusted analysis, risk of hospitalization for COVID-19 was higher with exposure to topicals or nonbiologics than with no exposure (HR 1.13, 95% CI 1.05–1.22, $P = 0.001$; HR 1.23, 95% CI 1.05–1.43, $P = 0.01$, respectively), absolute risk differences were 0.04% and 0.06%, respectively. Risk of hospitalization was not associated with exposure to biologics (Table 2).

A pseudo-cohort was obtained through use of the stabilized propensity score: distributions of patient characteristics were balanced, with standardized difference < 0.1 between the treatment classes (Figure S2; see Supporting Information). In the cause-specific conditional Cox proportional hazards model with IPTW, risk of hospitalization for COVID-19 was still associated with exposure to topicals or nonbiologics but not biologics [weighted HR (wHR) 1.11, 95% CI 1.04–1.20, $P < 10^{-2}$; wHR 1.27, 95% CI 1.09–1.48, $P < 10^{-2}$; wHR 1.04, 95% CI 0.83–1.31, $P = 0.83$, respectively, Table 2].

None of the exposures was associated with in-hospital mortality due to COVID-19 (Table 3).

Second study period

From 1 October to 31 December 2020, a total of 3603 patients were hospitalized for COVID-19: 727 (20.2%) with topical treatments, 163 (4.5%) nonbiologics, 73 (2.0%) biologics and 2640 (73.3%) unexposed. A total of 686 (19%) died in hospital from COVID-19: 139 (20.3%) with topical treatments, 22 (3.2%) nonbiologics, eight (1.2%) biologics and 517 (75.4%) unexposed. Mean time to hospitalization for COVID-19 was $1.26 (0.66)$ months.

The crude unadjusted analyses were similar to those from the first period (Tables 2 and 3). The absolute risk differences were: 0.07%, 0.1% and 0.03% for topicals, nonbiologics and biologics, respectively. In the cause-specific conditional Cox proportional hazards model with IPTW, risk of hospitalization for COVID-19 was associated with all groups of exposure vs. exposure (wHR 1.17, 95% CI 1.07–1.27, $P < 10^{-3}$; wHR 1.45, 95% CI 1.24–1.70, $P < 10^{-4}$ and wHR 1.44, 1.17–1.77, $P < 10^{-3}$ for topicals, nonbiologics and biologics, respectively, Table 2). None of the exposures was associated with in-hospital mortality due to COVID-19 (Table 3).

Subgroup analysis

Considering patients with psoriasis without comorbidities, we found that analyses did not differ from the main analyses except for patients receiving only topical treatments who were

Table 2 Risk of hospitalization with COVID-19 by study period and treatment group in the unadjusted Cox model and Cox model with inverse probability of treatment weighting (IPTW)

Treatment group	N (%)	Unadjusted Cox			IPTW Cox ^a		
		Crude HR	95% CI	P-value	wHR	95% CI	P-value
First period (February to June 2020), N = 1 326 312							
Unexposed	2602 (0.3)	–			–		
923 018							
Topicals	1025 (0.3)	1.13	1.05–1.22	0.001	1.11	1.04–1.20	$< 10^{-2}$
321 837							
Nonbiologics	171 (0.4)	1.23	1.05–1.43	0.01	1.27	1.09–1.48	$< 10^{-2}$
49 459							
Biologics	73 (0.2)	0.81	0.64–1.02	0.07	1.04	0.83–1.31	0.83
31 998							
Second period (October to December 2020), N = 1 289 962							
Unexposed	2640 (0.3)	–			–		
996 238							
Topicals	727 (0.3)	1.27	1.17–1.37	$< 10^{-4}$	1.17	1.07–1.27	$< 10^{-3}$
216 977							
Nonbiologics	163 (0.4)	1.36	1.16–1.60	0.0001	1.45	1.24–1.70	$< 10^{-4}$
45 176							
Biologics	73 (0.2)	0.87	0.69–1.10	0.25	1.44	1.17–1.77	$< 10^{-3}$
31 571							

IPTW (age, sex, comorbidities: major adverse cardiovascular events, hypertension, metabolic diseases, chronic obstructive pulmonary disease, hepatic diseases, cancers and neurological illnesses); CI, confidence interval; HR, hazard ratio; wHR: weighted HR. ^aAdjustment for age, deprivation index and area of residence.

Table 3 Risk of in-hospital mortality due to COVID-19 by study period and treatment group in the unadjusted Cox model and Cox model with IPTW

Treatment groups	N (%)	Unadjusted Cox			IPTW Cox ^a		
		Crude HR	95% CI	P-value	wHR	95% CI	P-value
First period (February to July 2020), N = 1 326 312							
Unexposed	527 (0.1)	–			–		
923 018							
Topicals	203 (0.1)	1.11	0.94–1.30	0.22	1.15	0.97–1.35	0.11
321 837							
Nonbiologics	25 (0.1)	0.88	0.59–1.32	0.55	1.02	0.67–1.54	0.94
49 459							
Biologics	4 (0)	0.22	0.08–0.58	0.22	0.54	0.24–1.23	0.14
31 998							
Second period (October to December 2020), N = 1 289 962							
Unexposed	517 (0.1)	–			–		
996 238							
Topicals	139 (0.1)	1.24	1.03–1.49	0.03	1.17	0.96–1.42	0.13
216 977							
Nonbiologics	22 (0.1)	0.94	0.61–1.44	0.77	1.27	0.83–1.94	0.27
45 176							
Biologics	8 (0)	0.49	0.24–0.98	0.04	1.49	0.87–2.57	0.15
31 571							

IPTW (age, sex, comorbidities: major adverse cardiovascular events, hypertension, metabolic diseases, chronic obstructive pulmonary disease, hepatic diseases, cancers and neurological illnesses); CI, confidence interval; HR, hazard ratio; wHR, weighted HR. ^aAdjustment for age, deprivation index and area of residence.

no longer at risk of being hospitalized with COVID-19 (Table 4).

Sensitivity analyses

During the first period, 9532 patients died (including 759 in-hospital deaths from COVID-19) and during the second period, 8379 (686 in hospital) died. Results from the Fine-Gray competing risks analyses did not differ from the main analyses (Tables S2 and S3; see Supporting Information). Results from the conventional adjusted multivariate Cox models and from treatment exposure defined within a 3-month period before the index date differed only for topical exposures (Table S3). Indeed, risk of COVID-19 in-hospital mortality was increased for patients exposed to topical treatments during the two periods compared with the global psoriasis population. Results from treatment exposures defined within a 9-month period before the index date did not differ from the main analysis, except for the risk of hospitalization for COVID-19 which was no longer associated with topical exposures in the first period (Table S3).

Discussion

In this study based on large nationwide, retrospective, 'exposed/unexposed' cohorts, exposure to systemic treatments for psoriasis including nonbiologic and biologic drugs did not increase the risk of in-hospital mortality due to COVID-19. These results were robust when using a variety of

methodological approaches to properly account for potential confounders, including an adjusted cause-specific Cox model, competing-risk analyses and propensity score-based approaches.

Several studies assessed the incidence of severe COVID-19 outcomes (hospitalization and death) in patients receiving systemic therapies for psoriasis during the pandemic.^{9,13,17} The authors gave a reassuring message, suggesting no increased risk of death due to COVID-19 for patients receiving biologic treatments for psoriasis. However, because of too-small study samples (from 374¹⁷ to 2329⁹ with psoriasis), the absolute number of patients who died from COVID-19 was very low (one to nine deaths in total), so interpretation of the results is cautioned. Our study provides results from large cohorts (> 1 000 000 with psoriasis) with a high number of events (> 8000 psoriatic patients hospitalized for COVID-19 leading to 1445 deaths across both study periods).

We found the risk of hospitalization for COVID-19 to be associated with exposure to nonbiologic treatments in raw and adjusted analyses, in the first and the second period of the study, compared with unexposed patients. However, nonbiologic treatment exposure was not associated with increased risk of in-hospital mortality due to COVID-19, and the fluctuation observed in sensitivity analyses can be explained by the low number of events.

Results for biologic therapy exposure are not so clear, except for the risk of mortality. Indeed, biologic therapy exposure did not increase the risk of in-hospital mortality due to COVID-19. Considering hospitalization for COVID-19, we

Table 4 Risk of hospitalization or in-hospital mortality for COVID-19 by study period and treatment group in subgroup analyses of patients with psoriasis without any comorbidities

IPTW Cox ^a Treatment group (ref. unexposed)	Risk of hospitalization with COVID-19				Risk of in-hospital mortality due to COVID-19			
	N (%)	wHR	95% CI	P-value	N (%)	wHR	95% CI	P-value
First period (February to June 2020), N = 667 043								
Unexposed	550 (0.1)	–			34 (0.01)	–		
Topicals	188 (0.1)	1.11	0.94–1.31	0.22	7 (0.01)	0.74	0.32–1.69	0.48
Nonbiologics	41 (0.2)	1.41	1.02–1.94	0.04	4 (0.02)	2.02	0.63–6.51	0.24
Biologics	22 (0.1)	1.11	0.72–1.70	0.65	0 (0)	–		
Second period (October to December 2020); N = 649 308								
Unexposed	476 (0.1)	–			38 (0.01)	–		
Topicals	107 (0.1)	1.14	0.92–1.42	0.22	5 (0.01)	0.67	0.24–1.85	0.44
Nonbiologics	42 (0.2)	1.95	1.41–2.71	< 10 ⁻⁴	2 (0.01)	1.77	0.42–7.43	0.44
Biologics	22 (0.1)	1.61	1.06–2.42	0.02	1 (0.01)	2.30	0.39–13.45	0.36

IPTW, inverse probability of treatment weighting (age, sex, comorbidities: major adverse cardiovascular events, hypertension, metabolic diseases, chronic obstructive pulmonary disease, hepatic diseases, cancers and neurological illnesses); CI, confidence interval; HR, hazard ratio; wHR, weighted HR. ^aAdjustment for age, deprivation index and area of residence.

found no association between biologic therapy exposure and risk of hospitalization for COVID-19 when considering the first study period coinciding with the first wave of the pandemic in France. However, during the second period, risk of hospitalization for COVID-19 was increased with exposure to biologic therapy in adjusted analyses. Mahil *et al.* highlighted the differences in risk-mitigating behaviours between the biologics/nonbiologics/no systemic agent groups.³¹ Indeed, individuals exposed to biologic treatments more frequently used shielding or self-isolating behaviours compared with other exposure groups. Thus, individuals exposed to biologic treatments were less likely to be at risk of COVID-19 and to die from it than other exposure groups, at least in the first part of the pandemic. As it was debated whether biologic agents should be discontinued to prevent severe complications of COVID-19 at the beginning of the pandemic, a change in treatment advice could also have occurred during the two periods. In fact, a decrease of up to 57% was observed in the initiation of biologics for psoriasis healthcare users during the first lockdown (March to May) in France, much higher than the one we observed during the second wave.²⁰ At the same time, patients already treated with biologics and nonbiologic systemic treatments maintained their treatments during the pandemic.²⁰ Cumulative reassuring data on the use of biologics during the COVID-19 pandemic may have changed patients' risk-mitigating and clinicians' prescription behaviours. A wider exposure to COVID-19 may have led to a similar risk of hospitalization for COVID-19 for individuals exposed to biologics than no biologics. The increased risk of hospitalization for COVID-19 for patients receiving a systemic treatment for psoriasis may reflect a population with better continuity of care within the healthcare system, leading to an increased chance of hospitalization. Our results did not support a prophylactic effect of long-term use of biologics on risk of hospitalization for COVID-19 or in-hospital mortality.

Lastly, we also found the risk of hospitalization for COVID-19 to be associated with exposure to topical treatments in raw and adjusted analyses, in the first and the second period of the study, compared with unexposed patients. Interestingly, when considering the subgroup of patients with psoriasis without any comorbidities, patients receiving only topical treatment were no longer at risk of being hospitalized for COVID-19 whereas patients receiving systemic treatments were. The higher risk of hospitalization for COVID-19 for patients with psoriasis with topical exposure in the main analysis may be related to the global profile of patients (including their comorbidities) rather than the exposure.

Among the strengths of our study is the large nationwide exhaustive study population. For hospitalization for COVID-19, we used information reported in an exceptional and accelerated way coordinated by public French authorities, Santé Publique France (the French centre comparable with the US Centers for Disease Control and Prevention), including approximately 94% of all patients (87 809 of 93 406) who were hospitalized for COVID-19 in France. However, our results cannot be generalized to asymptomatic or mild-to-moderate forms of COVID-19. Using the French health-insurance data and already-validated algorithms^{23–25,32} with an 85% estimated sensitivity,²⁴ we obtained a large study sample of patients with psoriasis, allowing for risk comparisons between exposures. Our definition of psoriasis was based on the prescription of at least two topical vitamin D derivatives within a 2-year period. These drugs constitute the first-line treatment for psoriasis,²³ and our definition has been validated in a study of a Danish health-insurance database by Egeberg *et al.*³² Although our definition was sensitive (85%),²⁴ it did not achieve the value of 98% reported by Egeberg *et al.*³² In the Danish study, patients with psoriasis were identified after the second prescription of topical vitamin D derivatives (albeit in the absence of a 2-year restricted period); this definition was used in addition to the ICD-10 codes for

psoriasis applied to inpatients and outpatients. Unfortunately, ICD-10 codes are not recorded for outpatients in the French database. Thus, our study probably underestimated the number of cases of psoriasis. However, any misclassification should have been similar for all types of drugs, and we are confident that our definition is specific. Firstly, our population received both topical and systemic treatments that are reimbursed in the context of psoriasis – thus minimizing selection bias. Secondly, our study population had much the same characteristics as previously described populations of patients with severe psoriasis.³³ Lastly, a recent systematic review validated the definition we used.²⁵ Causal interpretation of our findings relying on retrospective evaluation of medico-administrative data is still cautioned, considering the observational nature of the study design. In addition, residual confounding cannot be excluded.

To conclude, this study, involving a large nationwide sample, did not find an association between using systemic treatments for psoriasis (including nonbiologic and biologic drugs) and increased risk of in-hospital mortality due to COVID-19. The increased risk of hospitalization for COVID-19 for patients receiving a systemic treatment may reflect a population better caught by the healthcare system. These results provide evidence supporting a continuity of psoriasis care and maintaining the use of systemic treatment for psoriasis during the pandemic.

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References

- Guan W, Ni Z, Hu Y *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**:1708–20.
- Santé Publique France. Coronavirus: chiffres clés et évolution de la COVID-19 en France et dans le Monde [Internet]. 2021 [cited 9 Feb 2021]. Available from: <https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde#:~:text=nombre%20de%20passages%20aux%20urgences,19%20d%C3%A9clar%C3%A9es%20en%204h%203A%201> (last accessed 28 July 2021).
- Williamson EJ, Walker AJ, Bhaskaran K *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**:430–6.
- Abuabara K, Azfar RS, Shin DB *et al.* Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K.: cause-specific mortality in patients with severe psoriasis. *Br J Dermatol* 2010; **163**:586–92.
- Marques E, Paluch Z, Boháč P *et al.* Epidemiology of moderate-to-severe psoriasis: a comparison between psoriasis patients treated with biological agents, conventional systemic drugs and topical agents. *J Dermatol Treat* 2020; <https://doi.org/10.1080/09546634.2020.1826393>.
- Weill A, Drouin J, Desplas D *et al.* Usage des médicaments de ville en France durant l'épidémie de la Covid-19 – point de situation jusqu'au 13 septembre 2020 [Internet]. GIS Epi-Phare; 2020 Oct, p. 383. Report No. 4. Available from: <https://www.epi-phare.fr/rapports-detudes-et-publications/covid-19-usage-des-medicaments-de-ville-en-france-rapport4/> (last accessed 28 July 2021).
- Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**:2277–94.
- Afach S, Chaimani A, Evrenoglou T *et al.* Meta-analysis results do not reflect the real safety of biologics in psoriasis. *Br J Dermatol* 2021; **184**:415–24. <https://doi.org/10.1111/bjd.19244>.
- Baniandrés-Rodríguez O, Vilar-Alejo J, Rivera R *et al.* Incidence of severe COVID-19 outcomes in psoriatic patients treated with systemic therapies during the pandemic: a BIOBADADERM cohort analysis. *J Am Acad Dermatol* 2021; **84**:513–7.
- Balestri R, Rech G, Girardelli CR. SARS-CoV-2 infection in a psoriatic patient treated with IL-17 inhibitor. *J Eur Acad Dermatol Venereol* 2020; **34**:e357–8.
- Benhadou F, Marmol V. Improvement of SARS-CoV-2 symptoms following guselkumab injection in a psoriatic patient. *J Eur Acad Dermatol Venereol* 2020; **34**:e363–4.
- Conti A, Lasagni C, Bigli L, Pellacani G. Evolution of COVID-19 infection in four psoriatic patients treated with biological drugs. *J Eur Acad Dermatol Venereol* 2020; **34**:e360–1.
- Gisondi P, Zaza G, Del Giglio M *et al.* Risk of hospitalization and death from COVID-19 infection in patients with chronic plaque psoriasis receiving a biologic treatment and renal transplant recipients in maintenance immunosuppressive treatment. *J Am Acad Dermatol* 2020; **83**:285–7.
- Messina F, Piaserico S. SARS-CoV-2 infection in a psoriatic patient treated with IL-23 inhibitor. *J Eur Acad Dermatol Venereol* 2020; **34**:e254–5.
- Yousaf A, Gayam S, Feldman S *et al.* Clinical outcomes of COVID-19 in patients taking tumor necrosis factor inhibitors or methotrexate: a multicenter research network study. *J Am Acad Dermatol* 2021; **84**:70–5.
- Ward M, Gooderham M. Asymptomatic SARS-CoV2 infection in a patient receiving risankizumab, an inhibitor of interleukin 23. *JAAD Case Rep* 2021; **7**:60–1.
- Mahil SK, Dand N, Mason KJ *et al.* Factors associated with adverse COVID-19 outcomes in patients with psoriasis – insights from a global registry-based study. *J Allergy Clin Immunol* 2021; **147**:60–71.
- Gelfand JM, Armstrong AW, Bell S *et al.* National Psoriasis Foundation COVID-19 Task Force guidance for management of psoriatic disease during the pandemic: Version 2 – Advances in psoriatic disease management, COVID-19 vaccines, and COVID-19 treatments. *J Am Acad Dermatol* 2021; **84**:1254–68.
- Lebwohl M, Rivera-Oyola R, Murrell DF. Should biologics for psoriasis be interrupted in the era of COVID-19? *J Am Acad Dermatol* 2020; **82**:1217–18.
- Penso L, Dray-Spira R, Weill A *et al.* Drop in biological initiation for patients with psoriasis during the COVID-pandemic. *Br J Dermatol* 2021; <https://doi.org/10.1111/bjd.20406>.
- Tuppin P, Rudant J, Constantinou P *et al.* Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev D'Épidémiologie Santé Publique* 2017; **65**:S149–67.
- Tuppin P, Drouin J, Mazza M *et al.* Hospitalization admission rates for low-income subjects with full health insurance coverage in France. *Eur J Public Health* 2011; **21**:560–6.
- Mason AR, Mason J, Cork M *et al.* Topical treatments for chronic plaque psoriasis. *Cochrane Database Syst Rev* 2013; **3**:CD005028.
- Sbidian E, Mezzarobba M, Weill A *et al.* Persistence of treatment with biologics for patients with psoriasis: a real-world analysis of 16 545 biologic-naïve patients from the French National Health Insurance database (SNIIRAM). *Br J Dermatol* 2019; **180**:86–93.
- Castagné B, Viprey M, Caillet-Pascal P *et al.*; for groupe REDSIAM. Algorithmes d'identification des rhumatismes inflammatoires

- chroniques et du psoriasis dans les bases médico-administratives: revue de la littérature [Algorithms to identify chronic inflammatory rheumatism and psoriasis in medico-administrative databases: a review of the literature]. *Rev Epidemiol Sante Publique* 2021; **69**:225–33 (in French).
- 26 Revil H, Blanchoz J-M, Olm C, Bailly S. Renoncer a se soigner, Premiers résultats d'enquête [Internet]. Odenore/Assurance maladie; 2020 Dec. Available from: <https://www.ameli.fr/medecin/actualites/etude-odenore-pres-de-2-personnes-sur-3-ont-renonce-se-soigner-pendant-le-premier-confinement> (last accessed 28 July 2021).
- 27 Weill A, Drouin J, Desplas D *et al.* Usage des médicaments de ville en France durant l'épidémie de la Covid-19 – point de situation jusqu'au 25 avril 2021 [Internet]. GIS Epi-Phare; 2021 May, p. 300. Report No. 6. Available from: <https://www.epi-phare.fr/rapports-detudes-et-publications/covid-19-usage-des-medicaments-de-ville-en-france-rapport4/> (last accessed 28 July 2021).
- 28 Rey G, Jouglu E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997–2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. *BMC Public Health* 2009; **9**:33.
- 29 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34**:3661–79.
- 30 Xu S, Ross C, Raebel MA *et al.* Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2010; **13**:273–7.
- 31 Mahil SK, Yates M, Langan SM *et al.*; PsoProtect, CORE-UK study groups. Risk-mitigating behaviours in people with inflammatory skin and joint disease during the COVID-19 pandemic differ by treatment type: a cross-sectional patient survey. *Br J Dermatol* 2021; **185**:80–90.
- 32 Egeberg A, Mallbris L, Gislasen GH *et al.* Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *J Invest Dermatol* 2016; **136**:93–8.
- 33 Grodner C, Sbidian E, Weill A, Mezzarobba M. Epidemiologic study in a real-world analysis of patients with treatment for psoriasis in the French national health insurance database. *J Eur Acad Dermatol Venerol* 2021; **35**:411–6.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Definitions of exposures, associated inflammatory diseases and comorbidities.

Table S2 Risk of hospitalization with COVID-19 by study period and treatment group in sensitivity analyses.

Table S3 Risk of in-hospital mortality for COVID-19 by study period and treatment group in sensitivity analyses.

Figure S1 Flowchart of the psoriasis definition algorithm.

Figure S2 Standardized differences before and after inverse probability of treatment weighting.