





# Impact of COVID-19 Pandemic on Temporal Trends of Hemostasis Test in France: A Retrospective Analysis of 9 Years of National Health Data

Nûn K. Bentounes<sup>1,2</sup> Richard Chocron<sup>3,4</sup> Aurélien Philippe<sup>1,2</sup> David M. Smadja<sup>1,2,5</sup>   
Nicolas Gendron<sup>1,2</sup> 

<sup>1</sup> University Paris Cité, Innovative Therapies in Haemostasis, INSERM, Paris, France

<sup>2</sup> Hematology Department and Biosurgical Research Lab (Carpentier Foundation), Assistance Publique Hôpitaux de Paris. Centre-Université de Paris, Paris, France

<sup>3</sup> Emergency Department, Assistance Publique Hôpitaux de Paris. Centre-Université de Paris, Paris, France

<sup>4</sup> University Paris Cité, Paris Cardiovascular Research Center (PARCC), INSERM, Paris, France

**Address for correspondence** Dr. Nicolas Gendron, PharmD, PhD, Department of Hematology, European Hospital George Pompidou, 20 rue Leblanc, 75015 Paris, France (e-mail: nicolas.gendron@aphp.fr).

<sup>5</sup> French Clinical Research Infrastructure Network (F-CRIN), Investigation Network On Venous Thrombo-Embolic (INNOVTE), Saint-Étienne, France

TH Open 2023;7:e285–e288.

Coronavirus disease 2019 (COVID-19) emerged as a global pandemic associated with high rates of morbidity and mortality. To face this health crisis, the government had to resort to exceptional measures to stop the spread of severe acute respiratory syndrome coronavirus 2, notably two consecutive lockdowns in 2020. This greatly impacted the health care system, including a reduction in nonurgent care activities outside of COVID-19 and a massive deployment of tools to better manage COVID-19 patients,<sup>1</sup> particularly with the use of laboratory tests with diagnostic and prognostic values. In 2020, the French state health care budget recorded its highest annual deficit since its creation, at 36.8 billion euros.<sup>2</sup>

Beyond the context of COVID-19, laboratory tests occupy a central place in health care. Indeed, more than 70% of clinical decisions are influenced by test results, as are around 40% of primary care consultations.<sup>3</sup> Among laboratory tests, hemostasis tests are mainly used to (1) establish whether an individual is at risk of bleeding before an elective or urgent surgery or procedure, (2), monitor anticoagulant therapy, (3) diagnose specific conditions like coagulopathy and exclude venous thromboembolism (VTE)<sup>4</sup> or heparin-induced thrombocytopenia (HIT).

The aim of our study was to analyze temporal trends of hemostasis tests performed in France and the impact of the COVID-19 pandemic.

We collected the number of hemostasis test reimbursements each year in France using the French national health insurance database<sup>5</sup> from January 1, 2013 to December 31, 2021. This database included all reimbursed biological tests that were ordered for outpatients or hospitalized patients in private, for-profit health care facilities. We extracted the total yearly number of these tests: hemograms, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen, endogenous and exogenous factors, anti-FXa activity (unspecified on type of heparin used), von Willebrand Factor ristocetin cofactor activity (VWF:RCO), D-dimer, and anti-platelet factor 4-heparin antibodies (anti-PF4/H). We then calculated the total person-years using demographic assessments from the National Institute of Statistics and Economic Studies.<sup>6</sup> Crude rates of test use per 100,000 inhabitants per year were calculated for each year. First, to have a starting point and to be as free as possible from bias due to potential variations of these tests prior to COVID-19, we used the nonparametric Mann–Kendall pattern test to assess whether or not the time series data had a statistically significant trend between 2013 and 2019. Then, to evaluate the impact of COVID-19 emergence on selected tests, we performed descriptive statistics between the number of tests performed between 2019 and 2020 and between 2020 and 2021. Statistical analysis was performed using RStudio (version 4.1.1).

received  
July 19, 2023  
accepted after revision  
August 31, 2023  
accepted manuscript online  
September 1, 2023

DOI <https://doi.org/10.1055/a-2165-1249>  
ISSN 2512-9465.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Between 2013 and 2021, a total of 810,421,768 tests were collected for 600,602,171 patients. During the pre-COVID-19 era between 2013 and 2019, we noted a gradual increase per year in the number of hemograms (+15%,  $p < 0.01$ ), PT (+3%,  $p < 0.01$ ), fibrinogen (+9%,  $p < 0.01$ ), D-dimer (+247%,  $p < 0.01$ ), VWF:RCo (+64%,  $p < 0.01$ ), FVIII (+48%,  $p < 0.01$ ), FIX (+53%,  $p < 0.05$ ), FXI (+53%,  $p < 0.05$ ), and exogenous coagulation factors assays ordered per 10,000 habitants (respectively FII +279%,  $p < 0.01$ ; FV +358%,  $p < 0.01$ ; FVII +452%,  $p < 0.01$  and FX +442%,  $p < 0.01$ ), whereas the number of anti-Xa activity ( $p > 0.05$ ), PF4/H antibodies ( $p > 0.05$ ), and FXII ( $p > 0.05$ ) ordered per 10,000 habitants remained stable (►Fig. 1). In contrast, we observed a gradual decrease of INR (−42%,  $p < 0.01$ ), APTT (−3%,  $p < 0.05$ ) ordered per 100,000 habitants.

During the first two waves of COVID-19 in France in 2020, the number of test reimbursements sharply decreased compared with 2019, particularly for INR (−18%), APTT (−8%), PT (−6%), and fibrinogen (−4%). Conversely, D-dimer (+19%), anti-PF4/H (+2%), FVII (+27%), and FX (+31%) were the only tests to increase in 2020. Between 2020 and 2021, we highlighted an increase of hemograms (+7%), PT (+11%), fibrinogen (+9%), D-dimer (+19%), PF4/H antibodies (+34%).

Between 2000 and 2012, the use of anticoagulant therapy steadily increased in France, with the sales of oral anticoagulants doubling.<sup>7,8</sup> For years, prevention and treatment of VTE were restricted to the use of heparins and vitamin K antagonists, which both require biological monitoring through the anti-Xa and INR assays, respectively. Direct oral anticoagulants became the most frequently prescribed anticoagulant therapy during the last decade in France,<sup>9</sup> which could explain the progressive decrease in the prescription of INR and anti-Xa activity assays. However, the number of reimbursements for D-dimer assays is increasing and reaching unprecedented levels, as it has almost doubled since 2014. We can attribute this sharp increase in use of D-dimer assays to exclude diagnosis of pulmonary embolism (with an increased incidence<sup>10</sup>), to help clinicians decide whether to stop or continue anticoagulant therapy using recent scores.<sup>10,11</sup> In 2020, early in the pandemic, several studies have shown coagulopathy<sup>11</sup> and endotheliopathy<sup>12</sup> associated with high prevalence of VTE in severe COVID-19. Furthermore, high D-dimer levels at admission were associated with worsening, intensive care unit (ICU) referral and higher in-hospital mortality<sup>13–15</sup> and regardless of VTE occurrence.<sup>16</sup> Then, interim guidance by the International Society on Thrombosis and Haemostasis (ISTH)<sup>17</sup> suggested relying on D-dimer solely at admission to decide whether hospitalized patients with COVID-19 were at risk of worsening and probably need more aggressive critical care support. All in all, COVID-19 pandemic could explain this major increase of D-dimer since 2020 with a part of overtesting as a result of the ISTH guidance.<sup>13</sup> As critically discussed by Akima et al,<sup>18</sup> D-dimer testing has to be interpreted along with a whole clinical assessment.

During the first two waves of COVID-19 in France in 2020, the number of test reimbursements sharply decreased compared with 2019, particularly for INR, APTT, PT, and fibrinogen.

This can be explained by the lower activity related to the first lockdown of the COVID-19 pandemic, with a significant decrease in global surgical activity and related preoperative hemostasis tests in 2020 and the reorganization of non-ICU wards.<sup>16</sup> Nonetheless, the most striking decrease remains that of INR, which reflects that a significant number of patients were unable to monitor their INR in medical laboratories.

During the COVID-19 outbreak, the high frequency of VTE despite prophylactic therapy and thrombocytopenia led to numerous suspicions of HIT, which led to relative stability of anti-PF4/H. In a meta-analysis, Uaprasert et al<sup>19</sup> observed that the incidence of HIT in COVID-19 patients was comparable to those without COVID-19. Since mass vaccination campaigns started in December 2020, several thrombotic events following COVID-19 vaccination were reported,<sup>18</sup> as well as cases of vaccine-induced thrombotic thrombocytopenia (VITT)<sup>20,21</sup> characterized with the association of thrombocytopenia, thrombosis associated with the presence of platelet-activating anti-PF4/H antibodies following ChAdOx1 nCov-19 and Ad26.OV2.S(21) vaccination. All in all, VITT suspicion, misinformation (inadvertently inaccurate or incomplete information), and disinformation (deliberately and often maliciously misleading information)<sup>20,21</sup> about COVID-19 vaccine risk of thrombosis could explain the strong increase of the number of hemograms, D-dimer, and anti-PF4/H antibodies assays (+34%) in 2021, while it remained relatively steady over the past 7 years.

We acknowledge several limitations with the present study. First, these data reflect the global trend in the evolution of biology assays ordered for outpatients or hospitalized patients in private, for-profit health care facilities, since the data concerning public health care structures are not available. Previous studies have demonstrated increased laboratory testing in teaching hospitals, compared with nonteaching hospitals, due to medical trainees (resident physicians and medical students).<sup>22</sup> Second, these data allow policy makers to assess trends in test use, but we were unable to collect data to evaluate this temporal trend according to certain parameters such as sex, age, diseases, or indication/type of anticoagulant therapy, which could be useful to refine the data.

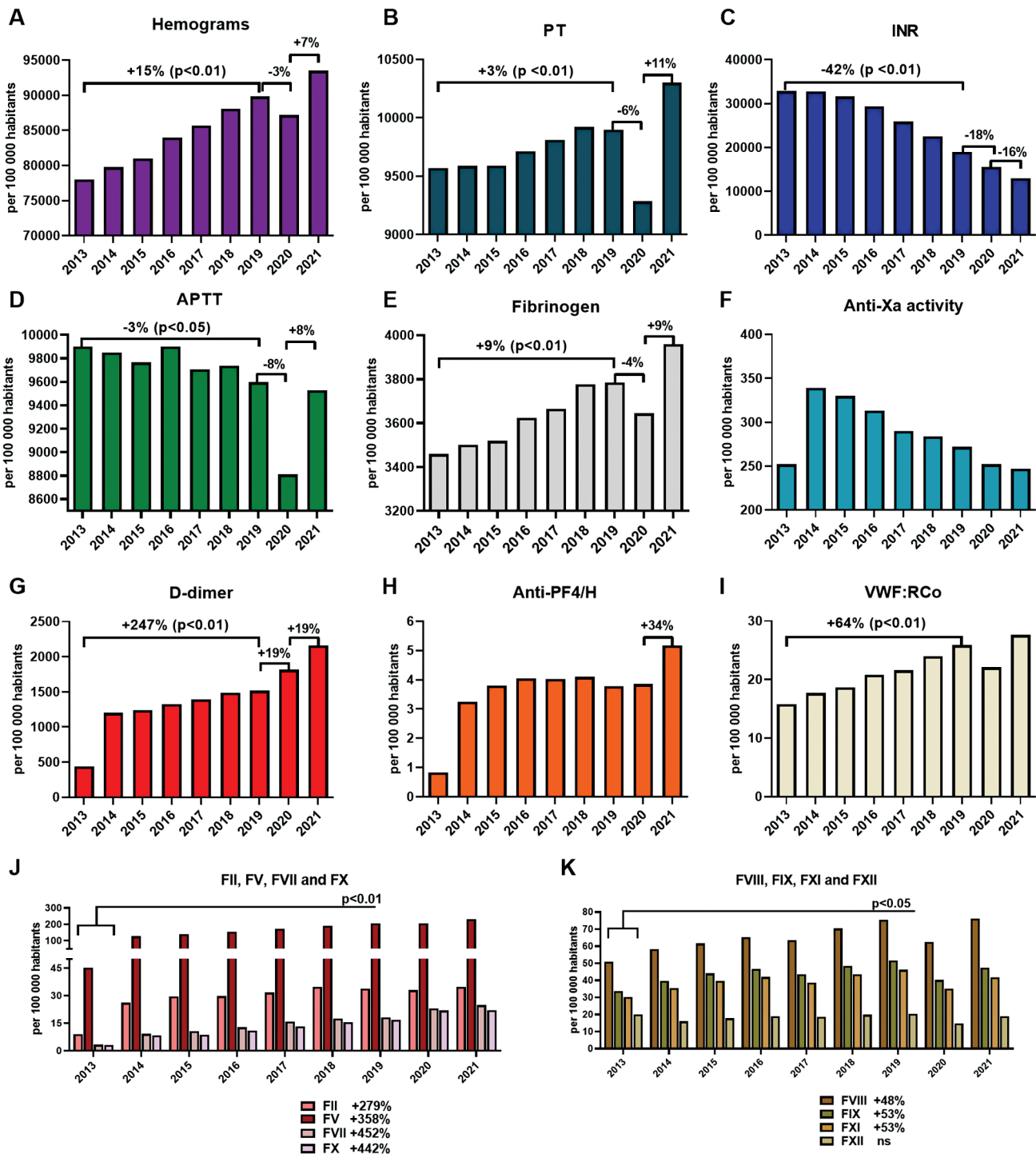
To conclude, the COVID-19 pandemic had a very important effect on hemostasis test trends, with a decrease in the majority of assays due to lockdowns and health care system reorganization but a strong increase in D-dimer assays due to COVID-19-associated coagulopathy, in association with hemograms and anti-PF4/H likely due to VITT suspicion and disinformation in 2021.

#### Author Contributions

N.K.B. and N.G. designed the project. N.K.B., R.C., and N.G. performed the analysis and analyzed the data. N.K.B., N.G., and A.P. wrote the paper. N.G. and D.M.S. supervised the work and reviewed the paper. All other authors reviewed the paper.

#### Funding

None.



**Fig. 1** (A) Hemograms (B) PT (C) INR (D) APTT (E) Fibrinogen (F) Anti-Xa activity (G) D-dimer (H) Anti-PF4/H (I) VWF:Rco (J) exogenous coagulation factors (K) endogenous coagulation factors. Temporal trends in France in total hemostasis tests use by test type between 2013 and 2021. Crude rates of test use per 100,000 habitants per year were calculated for each year. Anti-PF4/H, anti-PF4/heparin antibodies; APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; VWF:Rco, von Willebrand Factor ristocetin cofactor.

**Conflict of Interest**

D.M.S. and N.G. acknowledge the following without any relation with the current manuscript. D.M.S. received consultant, lecture fees, or travel awards from Carmat. N.G. discloses consulting fees or travel awards by Bayer, Bristol-Myers Squibb/Pfizer, and LEO-Pharma. All other authors have nothing to disclose.

**References**

- 1 OCDE L'impact territorial du Covid-19: Gérer la crise entre niveaux de gouvernement [Internet]. OECD. Accessed March 12, 2023 at: <https://www.oecd.org/coronavirus/policy-responses/l-impact-territorial-du-covid-19-gerer-la-crise-entre-niveaux-de-gouvernement-2596466b/>
- 2 Or Z, Gandré C, Durand Zaleski I, Steffen M. France's response to the Covid-19 pandemic: between a rock and a hard place. *Health Econ Policy Law* 2022;17(01):14–26
- 3 Lord Carter of Coles Report of the Review of NHS Pathology Services in England. 2006;1–51. 94.
- 4 Auditeau C, Khider L, Planquette B, Sanchez O, Smadja DM, Gendron N. D-dimer testing in clinical practice in the era of COVID-19. *Res Pract Thromb Haemost* 2022;6(04):e12730
- 5 L'Assurance maladie. Bases de données (Open Data) sur les dépenses d'assurance maladie [Internet]. 2021 Dec. Accessed at: <https://assurance-maladie.ameli.fr/etudes-et-donnees/parte-theme/depenses-assurance-maladie/bases-donnees-open-data-damir-depenses-assurance-maladie>
- 6 Insee. Bilan démographique 2021 - Insee Première n° 1889, janvier 2022 [Internet]. 2022 Jan. Accessed at: <https://www.insee.fr/fr/statistiques/6037741?sommaire=6036447>
- 7 Agence Nationale de sécurité du médicament et des produits de santé. Les anticoagulants en France en 2014 : état des lieux, synthèse et surveillance [Internet]. 2014. Accessed at: <https://documents.resip.fr/004127.pdf>
- 8 Haute Autorité Santé, Commission de la Transparence Rapport d'évaluation des médicaments anticoagulants oraux [Internet]. 2016 Sep. Accessed at: [https://www.has-sante.fr/upload/docs/application/pdf/2018-02/rapport\\_reev\\_aco\\_cteval234\\_2018-02-09\\_15-38-37\\_999.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2018-02/rapport_reev_aco_cteval234_2018-02-09_15-38-37_999.pdf)
- 9 Huiart L, Ferdynus C, Renoux C, et al. Trends in initiation of direct oral anticoagulant therapies for atrial fibrillation in a national population-based cross-sectional study in the French health insurance databases. *BMJ Open* 2018;8(03):e018180
- 10 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016;41(01):3–14
- 11 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135(23):2033–2040
- 12 Smadja DM, Mentzer SJ, Fontenay M, et al. COVID-19 is a systemic vascular hemopathy: insight for mechanistic and clinical aspects. *Angiogenesis* 2021;24(04):755–788
- 13 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–1062
- 14 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(04):844–847
- 15 Smadja DM, Bory OM, Diehl J-L, et al. Daily monitoring of D-dimer allows outcomes prediction in COVID-19. *TH Open* 2021;6(01):e21–e25
- 16 Chocron R, Duceau B, Gendron N, et al; Critical COVID-19 France investigators. D-dimer at hospital admission for COVID-19 are associated with in-hospital mortality, independent of venous thromboembolism: Insights from a French multicenter cohort study. *Arch Cardiovasc Dis* 2021;114(05):381–393
- 17 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18(05):1023–1026
- 18 Akima S, McLintock C, Hunt BJRE. RE: ISTH interim guidance to recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18(08):2057–2058
- 19 Uaprasert N, Tangcheewinsirikul N, Rojnuckarin P, et al. Heparin-induced thrombocytopenia in patients with COVID-19: a systematic review and meta-analysis. *Blood Adv* 2021;05:4521–4534
- 20 Barrière J, Frank F, Besançon L, et al. Scientific integrity requires publishing rebuttals and retracting problematic papers. *Stem Cell Rev Rep* 2023;19(02):568–572
- 21 Sule S, DaCosta MC, DeCou E, Gilson C, Wallace K, Goff SL. Communication of COVID-19 misinformation on social media by physicians in the US. *JAMA Netw Open* 2023;6(08):e2328928
- 22 Available at: 10.1001/jamainternmed.2017.6032