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RESEARCH ARTICLE

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Colchicine and risk of hospitalization due to COVID-19: A population-based study

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Abstract

Colchicine is one of the most widely studied and best-known anti-inflammatory treatments. This study aimed to assess the effect of colchicine on risk of hospitalization due to COVID-19; and its effect on susceptibility to and severity of the virus in patients with COVID-19. We carried out a population-based case-control study. The following groups were applied: (1) to assess *risk of hospitalization*, cases were patients with a positive PCR who were hospitalized due to COVID-19, and controls without a positive PCR; (2) to assess *susceptibility* to COVID-19, cases were patients with a positive PCR (hospitalized and non-hospitalized), and the same controls; (3) to determine *potential severity*, cases were subjects with COVID-19 hospitalized, and controls patients with COVID-19 nonhospitalised. Different electronic, linked, administrative health and clinical databases were used to extract data on sociodemographic variables, comorbidities, and medications dispensed. The study covered 3060 subjects with a positive PCR who were hospitalized, 26 757 with a positive PCR who were not hospitalized, and 56 785 healthy controls. After adjustment for sociodemographic variables, comorbidities and other treatments, colchicine did not modify *risk of hospitalization* due to COVID-19 (adjusted odd ratio [OR] 1.08 [95% confidence interval (CI) 0.76–1.53]), patients' *susceptibility* to contracting the disease (adjusted OR 1.12 (95% CI 0.91–1.37)) or the *severity* of the infection (adjusted OR 1.03 [95% CI 0.67–1.59]). Our results would neither support the prophylactic use of colchicine for prevention of the infection or hospitalization in any type of patient, nor justify the withdrawal of colchicine treatment due to a higher risk of contracting COVID-19.

KEYWORDS

colchicine, COVID-19, hospitalization, susceptibility

1 | INTRODUCTION

More than 2 years after the outbreak of the pandemic, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) continues to pose a threat to public health worldwide, despite the availability of vaccines.[1] The vaccine hesitancy,[2] low vaccination rates in some countries,[3] it remains of great relevance to identify existing treatments that can help mitigate the health impacts of COVID-19,[4,5] and to identify drugs that are associated with a worse outcome.

SARS-CoV-2 causes a wide variety of analytical alterations and clinical symptoms.[6] Disease progression is variable, ranging from asymptomatic states to death.[7] This virus activates innate immunity, and in cases where stimulation of the immunological system is excessive, it may trigger aberrant activation of inflammasome, excessive release of proinflammatory cytokines,[8] and neutrophil extracellular traps that prove toxic for lung epithelial cells.[9] This is in turn reflected as inflammation of the respiratory system, which leads to respiratory failure.[10]

With a view to preventing or reducing this exaggerated inflammatory response, a number of clinical trials have been conducted, using biological immunomodulatory agents[11] that inhibit various proinflammatory targets. It is in this context that colchicine is proposed as a possible therapeutic alternative. Colchicine is a widely studied and well-known drug. Its first use against pain and inflammation dates from 1500 B.C., thus ranking it as one of the most ancient anti-inflammatory treatments.[12] Extensive clinical experience with colchicine argues in support of its potential theoretical application to help control the development of COVID-19.[10] Although colchicine's action vis-à-vis this inflammatory response is less potent and specific,[12] its advantages over biological agents lie in its pleiotropic action, absence of immunosuppressive effect,[13] antiviral effect in in vitro studies,[13] oral dosage, price, and tolerance. There are therefore sufficient reasons for studying colchicine as a possible treatment for COVID-19.[7,14]

To date, the available evidence points to colchicine's role in preventing progression from an inflammatory activation stage to a hyperinflammatory stage, characteristic of patients in moderate-to-severe stages of the disease (stages II and III).[15–23] Even so, few studies envisage it being used as prophylaxis[24] or on nonhospitalised patients.[10,12,24] Studying how to prevent hospitalization due to COVID-19 would be a valuable strategy for conserving clinical resources and reducing healthcare costs.[12] Accordingly, we set out to assess: firstly, the effect of colchicine on risk of hospitalization due to COVID-19 in patients taking the medication on an ambulatory basis for another disease; and secondly, its effect on susceptibility to and potential severity of the virus in outpatients with COVID-19.

2 | METHODS

2.1 | Setting

This study was conducted in Galicia, a region in the north-west of Spain having a population of 2.7 million.

In Spain, 98% of citizens are covered by the National Health Service, which is largely funded by taxation, with patients being required to pay from 0% to 60% toward the cost of medications in line with their income.

The Galician Health Service (*Servicio Gallego de Salud/Servizo Galego de Saude/SERGAS*) comes under Spain's National Health Service and keeps electronic medical records (EMRs) on all patients. These EMRs register all information on clinical care provided at a primary and hospital level, and show data relating to income, medical visits, emergency visits, diagnostic tests, drug prescriptions, the Minimum Basic Data Set on hospital discharges, and the International Classification of Primary Care Codes, among other things.

2.2 | Study design and participants

We conducted a multiple case-population study, with an epidemiological approach.[25] The study population comprised all residents over the age of 18 years included in the Galician Health Service.

Three case-control sub studies were carried out. Specific definitions of cases and controls were applied for each of the study outcomes: hospitalization for COVID-19, susceptibility to COVID-19 and progression to severe disease.

- Case-control 1: To determine the influence of outpatient consumption of colchicine on *risk of hospitalization* due to COVID-19 (which may be due to a combination of susceptibility and severity), cases were defined as subjects with a positive PCR test result who were hospitalized at some *SERGAS* hospital across the period from the outbreak of the pandemic to 31 December 2020, inclusive. The time between the date of a positive PCR and hospitalization was set at a maximum of 10 days, to exclude possible cases which could have been admitted for reasons other than COVID-19 infection. Similarly, for study purposes, we excluded all persons who were not registered as residents of Galicia. To make up the control group, we selected a random sample of subjects without a positive PCR or any other COVID-19-positive diagnostic test result in 2020. We selected up to 20 controls for each case, matched by age, sex, and primary care referral service.
- Case-control 2: For the purpose of assessing the influence of outpatient consumption of colchicine on susceptibility to COVID-19 (defined as the risk of having a positive PCR test), a case was deemed to be any patient diagnosed with COVID-19 on the basis of a positive PCR in 2020 in Galicia, hospitalized or non-hospitalized, and controls were the same as those used in case-control 1, characterized by the absence of history of a positive PCR.
- Case-control 3: To determine the effect of outpatient consumption of colchicine on progression to severe disease (that requires hospitalization) in patients with COVID-19, we defined the group of cases as all cases diagnosed with COVID-19 who were hospitalized, and the control group as all patients diagnosed with COVID-19 who did not require hospitalization. In both groups, the diagnosis has to be confirmed by PCR in 2020 in Galicia.

2.3 | Data-source and -collection

All data were extracted semiautomatically by an independent information technology services company from the Complex Data-Analysis Systems (*Sistemas de Información y Análisis Complejos/SIAC*) used for *SERGAS*, which serve as a data warehouse whose designated purpose is to store and organize data by content (dispensing of medications, diagnoses, hospitalizations, etc.).

2.4 | Variables

The exposure variable was use of colchicine, prescribed and dispensed, in the three study groups across the 6 months preceding the index date (with this being defined as the 10 days before diagnosis of the disease). The indications for which colchicine is indicated in Spain are: (a) treatment of acute attacks of gout and chronic gout, (b) prophylaxis of acute attacks by initiation of treatment with uric acid mobilizers, (c) periodic illness (familial Mediterranean fever), and (d) treatment in adults of acute pericarditis and recurrent pericarditis.[26]

As our study covariates, we recorded demographic variables, anthropometric variables, comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, obesity, ischaemic heart disease, cerebrovascular accident, heart failure, atrial fibrillation, chronic renal failure, cancer, asthma), and exposure to all other medications prescribed and dispensed to each of the subjects in the 6 months before the index date.

The outcome variables assessed were: (i) hospitalization, defined as risk of hospitalization due to COVID-19 versus healthy controls; (ii) susceptibility, risk of PCR+ (hospitalized and nonhospitalised) versus not having COVID; and (iii) severity, risk of hospitalization among subjects with PCR+.

2.5 | Statistical analysis

Qualitative variables were expressed as frequencies and percentages, and quantitative variables as mean and standard deviation or median and interquartile range (IQR). Adjusted odds ratios (ORs) of hospitalization, severity and susceptibility, and their 95% confidence intervals (CIs) were calculated using generalized linear mixed models for binomial dependent variable (case vs. control).

The independent variable used to construct the models was dispensed versus absence of colchicine treatment. To assess risk of hospitalization, we considered individual observations as level 1, groups of cases and controls as level 2, and health area as level 3. In the case of the susceptibility and severity models, we considered individual observations as level 1, and health area as level 2. We have assumed that the effect of exposure on the probability of being a case (adjusted for covariates) could have been different between the different waves of contagion. For this reason, we include in the model a random effect (unstructured) indexed in each of the waves. Results were expressed in ORs with their 95% CIs, and adjustment was made for the above covariates.

Statistical significance was set at 0.05, and all statistical analyses were performed using the free R Statistical Software environment (version 4.1.0).

3 | RESULTS

To ascertain whether treatment with colchicine might have an influence on risk of hospitalization due to COVID-19, this study had a total of 86 602 subjects, comprising 3060 cases (subjects with a positive PCR who required hospitalization), 26 757 nonhospitalised cases (subjects with a positive PCR who did not require hospitalization), and 56 785 controls (subjects without a positive PCR).

The characteristics of the cohort are summarized in Table 1. While the median age (interquartile range/IQR) of the cohort of cases and controls was around 73 (59–84) years, in the group of patients with a positive PCR who did not require hospitalization, the median age (IQR) was around 47 (33–63) years. A higher prevalence of comorbidities and medicated subjects (angiotensin-converting enzyme inhibitors, lipid lowering drugs, anticoagulants, diuretics, nonsteroidal anti-inflammatory drugs, beta-blockers and colchicine) was observed among cases who required hospitalization than among the other groups (nonhospitalised cases and controls).

With respect to treatment with colchicine, Table 2 shows that, whereas 1.2% of cases had colchicine prescribed in monotherapy or in combination with dicycloverine before hospitalization, this percentage was lower in the control group (0.8%) and among cases with COVD-19 who did not require hospitalization (0.4%).

3.1 | Risk of hospitalization

With respect to the main study objective, while the crude estimates of risk of hospitalization due to COVID-19 suggested an increased risk among subjects who were taking colchicine—whether in monotherapy or combination therapy—in the previous 6 months (crude OR 1.46 [95%CI 1.04–2.05]), when adjustment was made for the covariates, the results suggested an absence of effect between colchicine use (in monotherapy or combination therapy) and risk of hospitalization due to COVID-19 (adjusted OR 1.08 [95% CI 0.76–1.53], $p > 0.05$).

3.2 | Risk of susceptibility

To analyze the risk of susceptibility of contracting COVID-19, we included 86,602 patients: of these, 29 817 were COVID-19 cases (hospitalized and nonhospitalised) and 56 785 were controls.

This model showed a higher proportion of controls (0.8%) with colchicine use than cases (0.5%), with a crude OR of 0.62 (95% CI 0.51–0.74). After adjusting for the other variables, however, the effect disappeared (adjusted OR 1.12 [95% CI 0.91–1.37]).

To assess the influence of the aetiological window on risk of hospitalization and susceptibility, different periods of exposure of 1,

TABLE 1 Baseline characteristics of study subjects

	Cases PCR + hospitalized (*n* = 3060)	PCR + nonhospitalized (*n* = 26757)	Controls (*n* = 56785)
Sex			
Male	1552 (50.7)	11122 (41.6)	28729 (50.6)
Female	1508 (49.3)	15635 (58.4)	28056 (49.4)
Age, median (IQR)	74 (59–84)	47 (33–63)	73 (59–84)
Health professional	81 (2.6)	1235 (4.6)	1260 (2.2)
Socio-health center resident	388 (12.7)	2118 (7.9)	3952 (7.0)
Comorbidities			
Hypertension	1754 (57.3)	6093 (22.8)	28020 (49.3)
Diabetes	841 (27.5)	2460 (9.2)	10920 (19.2)
COPD	398 (13.0)	730 (2.7)	4569 (8.0)
Obesity	889 (29.1)	3901 (14.6)	10817 (19.0)
Ischaemic heart disease	359 (11.7)	832 (3.1)	4768 (8.4)
Cerebrovascular accident	306 (10.0)	838 (3.1)	3874 (6.8)
Heart failure	469 (15.3)	639 (2.4)	4030 (7.1)
Atrial fibrillation	466 (15.2)	1035 (3.9)	5769 (10.2)
Chronic renal failure	437 (14.3)	678 (2.5)	4316 (7.6)
Cancer	529 (17.3)	1701 (6.4)	7770 (13.7)
Asthma	285 (9.3)	2152 (8.0)	3388 (6.0)
Current smoker	809 (26.4)	4036 (15.1)	8532 (15.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

TABLE 2 Results of risk of hospitalization, susceptibility, and severity

	Cases	Controls	Crude OR	Adjusted OR	*p* Value
Hospitalization					
Risk of hospitalization due to COVID-19 vs. healthy controls	36/3060 (1.2%)	459/56785 (0.8%)	1.46 (1.04–2.05)	1.08 (0.76–1.53)	0.678
Susceptibility					
Risk of PCR+ versus not having COVID	140/29817 (0.5%)	459/56785 (0.8%)	0.62 (0.51–0.74)	1.12 (0.91–1.37)	0.291
Severity					
Risk of hospitalization among subjects with PCR+	36/3060 (1.2%)	104/26757 (0.4%)	2.67 (1.79–3.99)	1.03 (0.67–1.59)	0.889

2, and 3 months were tested, but the conclusions did not change substantially.

3.3 | Risk of severity

With the aim of ascertaining whether colchicine reduced the risk of hospitalization in patients with a positive PCR, a statistical model was built that included 3060 cases (with a positive PCR who required hospitalization) and 26 757 controls (nonhospitalised subjects with a positive PCR). Observation showed that colchicine did not decrease the risk of hospitalization in patients with a positive PCR (adjusted OR 1.03 [95%CI 0.67–1.59]).

3.4 | Sensitivity analysis of the window of exposure

A number of analyses were performed to assess the effect of colchicine on risk of hospitalization due to COVID-19, taking into

TABLE 3 Risk of hospitalization, taking into account different windows of exposure to colchicine

	Cases $n = 3060$	Controls $n = 56\,785$	Crude OR	Adjusted OR	p Value
6 months	36 (1.2)	459 (0.8)	1.46 (1.04–2.05)	1.08 (0.76–1.53)	0.678
3 months	23 (0.8)	316 (0.6)	1.35 (0.88–2.07)	1.01 (0.65–1.56)	0.970
2 months	19 (0.6)	263 (0.5)	1.34 (0.84–2.14)	1.00 (0.62–1.61)	0.992
1 month	11 (0.4)	150 (0.3)	1.36 (0.74–2.52)	1.01 (0.54–1.89)	0.977

TABLE 4 Susceptibility, taking into account different windows of exposure to colchicine

	Cases $n = 29\,817$	Controls $n = 56\,785$	Crude OR	Adjusted OR	p Value
6 months	140 (0.5)	459 (0.8)	0.62 (0.51–0.74)	1.12 (0.91–1.37)	0.291
3 months	90 (0.3)	316 (0.6)	0.59 (0.47–0.75)	1.11 (0.86–1.44)	0.405
2 months	75 (0.3)	263 (0.5)	0.60 (0.47–0.75)	1.14 (0.87–1.50)	0.351
1 month	42 (0.1)	150 (0.3)	0.60 (0.43–0.83)	1.22 (0.84–1.77)	0.289

account the different windows of exposure (1, 2, 3, and 6 months). As will be seen, none of the windows showed any effect, whether for risk of hospitalization or for susceptibility (Tables 3 and 4).

4 | DISCUSSION

To our knowledge, this is the first study to use a large-sized population-based study with real world data (RWD) to analyze the effect of colchicine on COVID-19. Our results show that, after adjustment for comorbidities and other treatments, colchicine neither modifies the risk of hospitalization due to COVID-19 (OR = 1.08 (95% CI: 0.76–1.53), $p = 0.678$) or susceptibility to the virus, nor does it significantly affect disease severity among outpatients. Examples of a number of approaches used to assess the effect of colchicine on COVID-19 can be found in the literature:

(i) effect on susceptibility: a cohort of COVID-19-negative subjects is used to assess the impact of colchicine on the risk of being COVID-19 positive[24];
(ii) effect on severity: a cohort of COVID-19-positive subjects is used to assess whether colchicine has an effect on severity, as measured by the risk of being hospitalized[15];
(iii) effect on hospitalization: an initially COVID-19-free cohort of subjects is used to assess the impact of colchicine on hospitalizations due to COVID-19.[10] In this case, the effect observed makes it possible to assess the impact of colchicine on (i) and (ii) overall[10]; and,
(iv) efficacy/effectiveness on in-hospital COVID + patients: studies on patients with a medium-to-high level of severity are used to assess colchicine's effectiveness on disease progression (use of assisted respiration; intensive care unit; mortality).[15,16,27–31]

One of the great strengths of our design is that it allows for evaluation of the first three approaches in which there is less evidence.

We found only one study that analyzed risk of hospitalization (our main objective), that is, that undertaken by Madrid-García et al.[10] though this was conducted on a cohort of patients with rheumatological diseases and not on a general population cohort, as in our case. Their results show that prescription of colchicine had no influence on an increase or decrease in hospitalizations,[10] a finding in line with the results of our study.

With respect to the role of colchicine on susceptibility to infection, Omer Gendelman et al. studied colchicine's role as disease prophylaxis[24] but found no significant differences in colchicine use between controls and cases. After adjusting for covariates, we too were unable to detect any potential benefit of colchicine in terms of susceptibility to infection.

When it came to analyzing the risk of severity, our results once again showed no effect, a finding that is in line with the global results of the COLCORONA clinical trial,[15] which included 4488 subjects drawn from the general population, with diagnosis of COVID-19 based on microbiological (PCR+), clinical or epidemiological criteria. Whereas the global analysis of this trial also indicated that colchicine use failed to modify the risk of hospitalization (OR 0.79 (95% CI 0.60–1.03)), an analysis of the subgroup of patients diagnosed with PCR nonetheless showed a lower risk of hospitalization (OR 0.75 (95% CI 0.57–0.99),[15] something that is, in contrast to our results bearing in mind that the disease definition used was also PCR-based.

The meta-analysis performed by Gautambhai et al. on a total of 16 148 patients with COVID-19, studied the efficacy and safety of colchicine use in hospitalized and ambulatory patients versus a control group (which received any other treatment), though the only study included with ambulatory subjects was the above-mentioned COLCORONA study. Based on a moderate level of evidence, this meta-analysis concludes that there is no benefit to be had from the addition of colchicine to the standard treatment in patients with COVID-19.[32]

To our knowledge, there are currently 3 clinical trials in phase 3 (NCT04322682 (*COLCORONA*)[15]; NCT04350320 (*COL-COVID*)[17];

and NCT04328480 (*The ECLA PHRI COLCOVID Trial*)[30]), and another 3 in phase 2 (NCT04326790 (*GRECCO-19*)[18,27]; NCT04355143 (*COLHEART-19*)[28]; and NCT04322565[29]). All these studies (except COLCORONA, NCT04322682) evaluate the risk of clinical deterioration in patients hospitalized due to COVID-19, so that the results of our study are not comparable to them. Our study examines the effect of colchicine use on the early stages of the disease, that is, from prophylaxis to risk of hospitalization, where colchicine shows no effect on the modification of these events. That said, however, most clinical trials conducted to date focus on the action of colchicine on already hospitalized patients, in which the disease is at a stage of hyper-inflammatory activation. It is in these studies in which less clinical deterioration is observed among patients receiving colchicine-related treatment.[18,27]

This difference might be due to the fact colchicine exerts greater action in the disease stages in which an inflammatory response takes place, namely, stage II, where viral multiplication and inflammation is localized in the lung, and stage III, where systemic hyper-inflammation develops.[33–35] Our results and those of Alfredo Madrid-García et al.[10] and the COLCORONA trial[15] would appear to indicate that colchicine exhibits no effects on stage I of the disease, in which the inflammatory mechanisms have not yet been set in motion.

4.1 | Limitations and strengths of the study

Our study furnishes robust data on the effects of colchicine use on the first stages of COVID-19. This is due to its being a population-based, nested case-control study with a large sample size, which made it possible for narrow CIs to be obtained.

These results may be very relevant, in view of the fact that this is an RWD-based study. This type of study uses data generated by real clinical care, without any experimental allocation of treatment.[36] Studies based on RWD in real settings are indispensable for carrying out research on medications and improving clinical care. They make it possible to ascertain the effectiveness and safety of intangible factors (drug properties, personal attributes, and healthcare delivery processes) which generally require long-term experience and arduous research efforts.[37]

Furthermore, our study was adjusted for a number of confounding variables, such as comorbidities, use of other medications, and sociodemographic factors. We feel that our drug-exposure data enjoy a high validity, due to the fact that they were sourced from an administrative medication-dispensing database, which ensures that practically 100% of medications acquired from pharmacies are recorded. Indeed, it is this that lends our data an additional advantage, in contrast to other data sources that are prescription-based.

Then again, the fact that this was an observational study with secondary databases means one cannot rule out the possibility of there being confounding variables which may not have been measured or some misclassification of these.

Although, we had records of the main comorbidities linked to a higher risk of hospitalization due to COVID-19, there were no data on their degree of severity, something that could generate some type of residual confounding. Despite the fact that our results were based on pharmacy-dispensed medications, there is no way of ascertaining whether all the medications acquired from pharmacies were in fact consumed, since this is influenced by patients' degree of therapeutic adherence. There is also the possibility of unregistered treatments being provided (e.g., concomitant over-the-counter drugs or private healthcare prescriptions), but we feel that this does not amount to a major limitation since 98% of the Galician population is covered by the region's Public Health Service.

On the other hand, the hospitalization variable is a combination of susceptibility and severity variables, which could be affected by the changeability of the clinical criteria of the physicians who make the decision to hospitalise or not. However, this is an outcome variable that has been routinely used in observational studies[38,39] and even RCTs[40,41] to assess the effect of different exposures (drugs and vaccines) on COVID-19. Another possible limitation of our work is that the data were collected during 2020, when vaccination had not yet started and the most frequent variants in our setting were variants of the group known as 19B.[42] However, we have no reason to believe that the effect of colchicine against covid-19 is altered by the variants or the presence of the vaccine.

4.2 | Conclusions and implications

In summary, our results would neither support outpatient colchicine use to prevent infection or hospitalizations due to COVID-19, nor justify the withdrawal of colchicine treatment owing to a higher risk of contracting COVID-19. Further studies are needed to furnish more evidence on the matter, but based on our study data, prophylactic use of colchicine can neither be indicated nor recommended to prevent infection or hospitalization in any type of patient, including those who might have risk factors of a poor prognosis if they were to contract the disease.

AUTHOR CONTRIBUTIONS

María Sáenz-Aldea: Writing original draft preparation. **Ángel Salgado-Barreira**: Conceptualization, methodology, Writing – review and editing. **Margarita Taracido Trunk**: Writing original draft preparation, review and editing. **María Piñeiro-Lamas**: Formal analysis. **Maria T. Herdeiro**: Methodology, Writing – review and editing. **Manuel Portela-Romero**: Methodology, Writing – review and editing. **Marc Saez**: Visualization, Writing – review and editing. **Adolfo Figueiras**: Conceptualization, methodology, funding acquisition, Writing – review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

The study was approved by the Galician Clinical Research Ethics Committee (*Comité de Ética de Investigación de Galicia*), classified by the Spanish Agency of Medicines and Medical Devices (*Agencia Española del Medicamento y Productos Sanitarios/AEMPS*), and carried out in line with the Helsinki Declaration principles and the prevailing legislation governing biomedical research. The study protocol was registered at the EU Electronic Register of PostAuthorisation Studies, EUPAS44587, and is available from https://www.encepp.eu/encepp/viewResource.htm?id=44588. The data were extracted and processed on an anonymised basis, thereby ensuring subjects' confidentiality and privacy at all times.

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