Outcomes in treatment-resistant schizophrenia: symptoms, function and clozapine plasma concentrations

Amir Krivoy, Eromona Whiskey, Henrietta Webb-Wilson, Dan Joyce, Derek K. Tracy, Fiona Gaughran, James H. MacCabe and Sukhwinder S. Shergill

Abstract

Background: Clozapine is the only medication licenced for treating patients with treatment-refractory schizophrenia. However, there are no evidence-based guidelines as to the optimal plasma level of clozapine to aim for, and their association with clinical and functional outcome.

Objective: We assessed the relationship between clinical and functional outcome measures and blood concentrations of clozapine among patients with treatment-refractory psychosis.

Methods: Data were reviewed in 82 patients with treatment-refractory psychosis admitted to a specialised tertiary-level service and treated with clozapine. Analysis focussed on the relationship between clozapine and norclozapine plasma concentrations and the patient's clinical symptoms and functional status.

Results: Clinical symptom improvement was positively correlated with norclozapine plasma concentrations and inversely correlated with clozapine to norclozapine plasma concentrations ratio. Clozapine concentrations showed a bimodal association with clinical improvement (peaks around 350 and 660 ng/ml). Clinical symptom improvement correlated with functional outcomes, although there was no significant correlation between the latter and clozapine or norclozapine plasma concentrations.

Conclusion: Clozapine treatment was associated with optimal clinical improvement at two different peak plasma concentrations around 350 and 650 ng/ml. Clinical improvement was associated with functional outcome; however, functionality was not directly associated with clozapine concentrations. A subset of patients may require higher clozapine plasma concentrations to achieve clinical improvement.

Keywords: psychosis, clozapine, norclozapine

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Introduction

Clozapine is the most effective antipsychotic in treating refractory schizophrenia, but only about 50% of patients respond to treatment.[1] No consistent reliable predictor of response has yet been identified.[2] Previous studies suggest a relationship between clozapine plasma concentrations and therapeutic response[3,4] and a threshold of 350 ng/ml has often been proposed as necessary to achieve an adequate response.[5–8] Many schizophrenia treatment guidelines, including the Maudsley Prescribing Guidelines and those of the National Institute for Health and Clinical Excellence (NICE) and the British Association for Psychopharmacology (BAP), recommend plasma level monitoring with the aim of achieving concentrations equal to or greater than 350 ng/ml.[9] Yet substantial conflicting data exist regarding any relationship between clozapine plasma concentrations and therapeutic response.[10–12]

However, clinical symptomatic response to antipsychotic treatment by itself is not an adequate outcome measure in refractory schizophrenia.

Defining satisfactory outcomes in this heterogeneous population is much more challenging and multifaceted.[13] More recently, there has been a greater focus on improving functional outcomes in these patients, acknowledging that social and functional improvement is not necessarily linked with symptomatic improvement.[14] There is increasing recognition of the essential role of psychosocial, vocational, environmental and functional parameters in the subjective journey towards recovery.[15] Symptom reduction is often considered necessary but not sufficient to achieve recovery[16] – whose meaning is uniquely individual but frequently touches upon domains of functioning adequately to be able to be independent, to live in the community and to work and have personally meaningful relationships.

Clozapine is metabolised into an active metabolite *N*-desmethylclozapine (norclozapine), and this has been suggested to contribute to the overall superior efficacy of the drug.[17] Norclozapine is recognised to have a different pharmacological profile to clozapine at some receptor sites. A range of studies have investigated the effects of both the parent drug and the metabolite on muscarinic receptors and have shown that, unlike clozapine which acts as an antagonist at M1 receptors, norclozapine is a potent partial agonist.[18,19] This unique property of norclozapine may confer the procognitive effects sometimes observed in some clozapine-treated patients. The ratio of clozapine to its metabolite norclozapine may therefore have important clinical significance; some studies have suggested that the ratio of the parent drug clozapine to norclozapine may predict clinical outcomes.[20–22] However, a recent comprehensive review[18] suggests that the clozapine to norclozapine ratio does not predict clinical outcomes, although any effect on cognition still remains unclear (Table 1).

The National Psychosis Service (NPS) is a tertiary referral centre within the South London and Maudsley National Health Service (NHS) Foundation Trust (SLaM) located in London. It specialises in the treatment of patients with refractory psychotic disorders. In our previous study,[23] we examined outcomes of 325 patients discharged from the unit between 2001 and 2017. In this study, we examine the relationship between clozapine and norclozapine plasma concentrations and therapeutic response – specifically with respect to clinical symptomatic and functional outcomes. Our hypotheses were that clozapine concentrations greater than 350 ng/ml would be related to improved clinical and functional outcomes.

Methods

Population

We retrospectively examined clinical effectiveness outcomes of all consecutive admissions discharged with clozapine treatment between 2008 and 2017 from the NPS, SLaM. Data on clinical symptoms and occupational functioning were extracted from a cohort of 172 medical records of patients admitted between these years (mean age 33.6 years, SD = 12.1, 51.7% men), which has been described earlier.[23] From this dataset, only patients who had been discharged with clozapine treatment and had clozapine plasma concentrations at discharge were included in this study. The study was performed as part of an audit and approved by the Clinical Academic Group of SLaM, UK.

Medical records were reviewed by four independent medical raters affiliated to the team, with demographic and clinical data extracted using the operational criteria (OPCRIT) system; two occupational therapists used the Model of Human Occupation Screening Tool (MoHOST)[24,25] to extrapolate occupational functioning. Inter-rater reliability was optimised by common rating of a set of 10 different medical records and discussion around any differences; any subsequent uncertainties in any ratings were resolved by the senior author (SSS). All participants had a psychotic disorder, most of them met the International Classification of Diseases, Tenth Edition (ICD-10) criteria for a primary diagnosis of schizophrenia – the detail of patient characteristics referred to the unit are described elsewhere.[23,26] The only exclusion criteria for patient admission to the NPS are if there is a substantial risk of physical aggression, or if they have comorbid severe substance dependence disorders.

Variables

The OPCRIT is a widely used, reliable and validated tool to extract symptom-level data from medical records,[27] utilising an inventory of psychopathological symptoms, demographics and disease course variables that are scored with algorithms for clinical diagnosis.[28] The medical records on admission to, and discharge from, the

NPS were assessed to yield OPCRIT mental state examination severity scores for each time point, across five domains. Each symptom domain score is ordinal (with zero indicating an absence of those symptoms and higher values indicating increasing symptom severity): affective symptoms (16 items – maximum score 58), abnormal perceptions (6 items – maximum score 12), abnormal beliefs (18 items – maximum score 41), speech and thought disorders (6 items – maximum score 13) and appearance and behaviour (9 items – maximum score 24). Demographic information was collated for all participants, and medications, including dose, on admission and discharge were recorded.

The MoHOST[24,25] was employed by the specialist occupational therapists of the NPS at two time points – beginning of admission and before discharge. The MoHOST is an assessment tool that allows the therapist to gain an overview of the occupational functioning. It addresses motivation for occupation, pattern of occupation, communication, process and motor skills, and how the environment supports the person to participate in occupation. It consists of 24 items, four for each of the following six sections: volition (or 'motivation for occupation'), habituation (or 'pattern of occupation'), communication and interaction skills, process skills, motor skills and environment. These items are all rated using the same 4-point, ordinal, rating scale: the therapist rates each item as to whether the factor represented by the item facilitates (F) = 4, allows (A) = 3, inhibits (I) = 2 or restricts (R) = 1 the person's occupational participation. Each rating has specific descriptors that guide the selection of an appropriate rating. Thus, the rating process generates a profile of strengths and weaknesses affecting occupational participation, in addition to generating a measure of the client's occupational participation.

Clozapine plasma concentrations and norclozapine concentrations are routinely measured during an admission to the NPU. Plasma samples are taken from antecubital vein during morning time (0700–0800) at 12-h postdose trough levels. The plasma concentration at discharge from the NPS, which represented the optimal dose for an individual patient, was used in the analyses. Venous blood samples (3 ml) were transported to a central laboratory at King's College Hospital where liquid chromatography (LC) with tandem mass spectrometry (LC-MS/MS)[29] was performed within 72 h.

Table 1. Demographic and clinical features of the study sample (*N* = 82)..

	Mean/*N*	SD/%
Age (years)	37.7	12
Males	53	54.1
Length of stay (days)	392.2	231.6
Clozapine monotherapy on discharge	56	57.1
Clozapine level (ng/ml)	528.3	216.6
Norclozapine level (ng/ml)	296	132.3
Clozapine/Norclozapine ratio	1.93	0.8
Clozapine dose discharge (mg/day)	463.7	210.2
Clozapine dose admission (mg/day)	458.7	206.9
OPCRIT total change ratio (%)	44.2	41.6
A&B change ratio (%)	48.8	60
Speech change ratio (%)	34.3	52.2
Mood change ratio (%)	54.4	46.3
Belief change ratio (%)	27.3	39.8
Perception change ratio (%)	25.9	46.3

A&B, appearance and behaviour; OPCRIT, operational criteria.

Statistical analysis

OPCRIT scores were calculated for each of the five symptom domains. To overcome missing data of specific items in the domains, we calculated each domain score as a mean of available items (i.e. not missing). Total score was calculated as the mean of all five domains' scores. For each group, the change in the total OPCRIT score was calculated as % (baseline score − discharge score)/(baseline score). Association of clinical severity change during admission and functional score (MoHOST total score and domains) was examined using a linear regression model adjusted for length of stay and MoHOST baseline scores. Association of clozapine or norclozapine plasma concentrations or their ratio and clinical severity change was also examined using a linear regression model, adjusted for length of stay.

Results

A total of 98 patients (57% of the sample) were discharged from the NPU with clozapine treatment; of these, only 24 (24.5%) were treated with

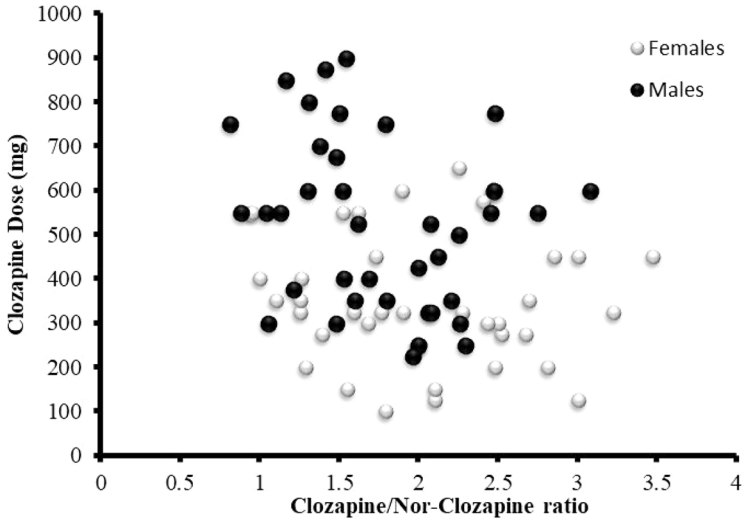

Figure 1. A scatter plot of clozapine daily dose and the ratio between clozapine and norclozapine plasma concentrations, stratified by sex.

clozapine on admission. At discharge, 56 (57.1% of clozapine-treated patients) were on clozapine monotherapy. Among patients, 45 (46%) were women, the mean age was 37.7 ± 12 years and mean length of hospitalisation was 392 ± 231 days.

Clozapine and norclozapine plasma concentrations

Among the 98 individuals discharged with clozapine, there were 82 (83.7%) recorded clozapine plasma concentrations at the time of discharge (mean 528.3 ± 216.5 ng/ml, range 100–1180 ng/ml). Distribution of results showed that 17 (21%) had concentrations below 350 ng/ml, 36 (44.4%) had concentrations between 350 and 600 ng/ml, 23 (28.4%) had concentrations between 600 and 800 ng/ml and 5 (6.2%) had concentrations above 800 ng/ml. Recorded plasma concentrations of norclozapine (mean 302 ± 132.8, range 30–780) and the ratio of clozapine/norclozapine (mean 1.93 ± 0.78) showed that only 15% of the sample had ratio less than 1.2 which may be suggestive of rapid metabolism,[20] while 70% had a ratio above 1.5.

There was no significant correlation between clozapine dose on discharge and clozapine or norclozapine plasma concentrations; however, the clozapine/norclozapine ratio was negatively correlated to dose ($r = -0.25$, $p = 0.03$), as shown in Figure 1.

The MoHOST functionality score

Mean scores of the MoHOST items and total score on admission and discharge are shown in Figure 2. From admission to discharge, the patients' total score increased by mean of 20.1% (median 15%). Within this, motivation for occupation increased by 28.1%, pattern of occupation increased by 37.7%, communication and interaction skills increased by 22.6%, process skills increased by 26.5% and motor skills increased by 6.9%. Unsurprisingly, there was little change in the inpatient environment (a minor decrease of 3.6%).

Effect of sex, age and length of stay

There was a difference between men and women in clozapine dose at discharge (543.27 ± 207.8 mg *versus* 369.66 ± 172.2 mg, $t = 4.4$, $p < 0.0001$, respectively); however, there were no sex differences in clozapine or norclozapine plasma concentrations, their ratio or measurement of clinical severity. There was also a sex difference in age (women 41.7 ± 12.63 years *versus* men 34.23 ± 10.35 years, $t = -3.2$, $p = 0.002$). There were no differences in sex with regard to length of stay, or the MoHOST score on discharge. Length of stay was inversely correlated with discharge MoHOST score ($r = -0.22$, $p = 0.038$). In a linear regression model, age, sex and length of stay were not significant predictors of the MoHOST score at discharge.

Clinical status change and functionality

The OPCRIT total score change ratio (i.e. between discharge to admission) was significantly correlated with MoHOST total score on discharge (Pearson's $r = 0.32$, $p = 0.004$) and the following items: communication and interaction skills ($r = 0.3$, $p = 0.005$), process skills ($r = 0.34$, $p = 0.003$) and motor skills ($r = 0.23$, $p = 0.04$).

Clinical status change and clozapine plasma concentrations

Change of OPCRIT scores was significantly correlated with norclozapine concentrations ($r = 0.23$, $p = 0.044$) and negatively correlated with the clozapine/norclozapine ratio ($r = -0.25$, $p = 0.027$) but not with clozapine plasma concentrations ($r = 0.11$, $p = 0.33$). A linear regression model adjusted for length of stay also showed a significant association between OPCRIT change and norclozapine level ($B = 0.074$, $t = 2.09$, $p = 0.04$) and an inverse

association with the clozapine/norclozapine ratio ($B=-0.48$, $t=-2.25$, $p=0.027$). However, a plot of clozapine plasma level (by deciles) and clinical change (OPCRIT) as depicted in Figure 3 showed a bimodal curve. Two peaks of optimal clinical improvement were noted – one at a level of 350 ng/ml and the other at a level of 650 ng/ml. It can be seen that deciles 1–3 (clozapine concentrations between 0.22 and 0.4 ng/ml) and 7–10 (clozapine concentrations between 0.61 and 0.94 ng/ml) were associated with increased clinical improvement of 40% and more. There was no difference between the two groups (deciles 1–3 and 7–1), with regard to sex, age, clozapine monotherapy, clozapine on admission or length of stay.

Functionality and clozapine plasma concentrations

There was no significant correlation between total MoHOST score and clozapine concentrations, norclozapine concentrations or their ratio.

Discussion

In this study, we examined the association between clozapine and norclozapine plasma concentrations with measures of clinical symptoms and functional improvement among patients with refractory psychosis admitted to a specialised unit. We hypothesised that a plasma level of above 350-ng/ml clozapine will be associated with the highest level of improvement in clinical severity and functional activity. Our main findings were that clozapine concentrations showed a pattern of bimodal association (350 and 660 ng/ml) with maximal clinical symptomatic improvement, and the level of plasma norclozapine and the ratio of clozapine to norclozapine were both also associated with clinical improvement. Although the clozapine level was not significantly associated with any functional measure, the clinical symptomatic improvement and functionality (especially communication, interaction and process skills) were found to be correlated with each other. This supports the importance of psychosocial, environmental and occupational inputs to complement any clinical symptomatic improvement derived from medication use.

There was a positive outcome for patients receiving inpatient treatment at the NPS, as reflected by the change in placement between admission and discharge. Most patients were discharged to more independent living than they were in before admission to the NPS, supporting the assumption that

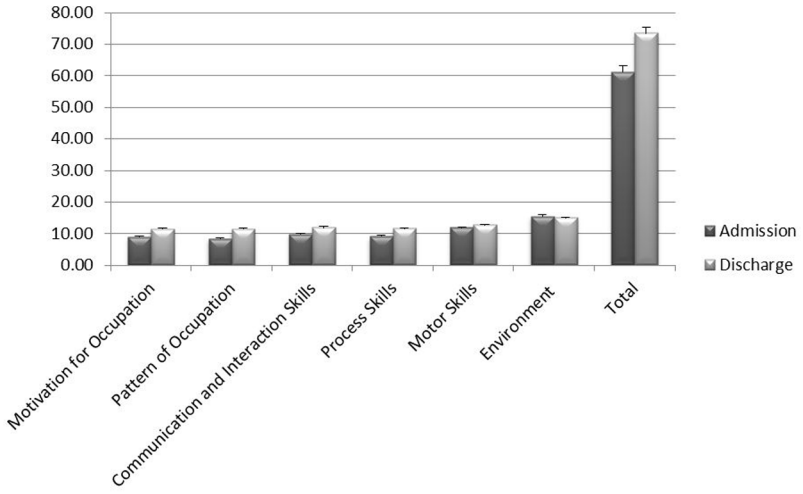

Figure 2. Mean scores of MoHOST functional measure at admission and discharge.
MoHOST, Model of Human Occupation Screening Tool.

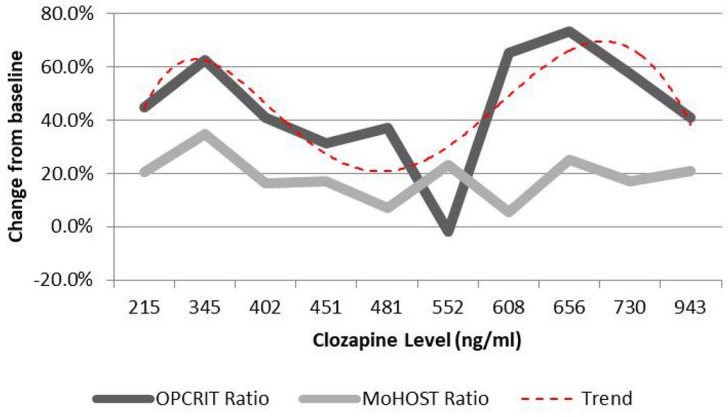

Figure 3. The association between plasma clozapine concentrations, binned to deciles, and symptomatic improvement and functional change during admission, as depicted by OPCRIT and MoHOST score change, respectively, from admission to discharge.
MoHOST, Model of Human Occupation Screening Tool; OPCRIT, operational criteria.

the prescribed pharmacotherapy at discharge (in combination with the psychosocial interventions) represents their optimal treatment. However, given the NPS is an inpatient service – set within a hospital environment – although the symptomatic clinical presentation may be significantly improved at discharge, further rehabilitation in specialised community-based settings would often be necessary to optimise the change in functional and occupational outcomes.

Clozapine dose was inversely correlated with the ratio of clozapine/norclozapine (Figure 1), rather

than with clozapine plasma concentrations, suggesting it to be the expression of clozapine pharmacokinetics. While sex dosing was different (men higher), concentrations and outcomes were similar, suggesting that the dosing is primarily a function of pharmacokinetics, and typically larger body mass of male patients. Sex distribution of the clozapine/norclozapine ratio in Figure 1 may suggest that the potential for saturation of the pathway at a lower dose in women may result in raising the ratio.

In this unique sample of treatment-refractory psychosis patients, there was a linear correlation between the magnitude of symptomatic improvement and the level of norclozapine at discharge and the ratio between clozapine and norclozapine. Previous studies have demonstrated mixed results with regard to this relationship; the norclozapine level was associated with positive cognitive performance, mainly short-term memory.[30] This effect was attributed to the compound's inverse effect on muscarinic receptor[17] and more specifically M1. A more recent review[18] found a weighted mean clozapine/norclozapine ratio of 1.73 in 2317 adult patients from 19 studies, with the range in their studies varying widely between 1.19 and 3.37. They report that the clozapine/norclozapine ratio was not associated with clinical response. The association of the clozapine/norclozapine ratio with cognitive measures was found to be more uncertain with four cross-sectional studies that were positive and a post hoc analysis of a randomised clinical trial that was negative.

There is no robust evidence-based consensus regarding the optimal therapeutic serum level of clozapine, with popular expert guidance suggesting that a minimum level of 350 ng/ml is necessary to elicit any beneficial effect.[9,12,31] However, other data suggest that a subset of patients will require a higher serum level to achieve a robust reduction of their symptoms, whereas others found a lower threshold for response[32] around 200 ng/ml. Therefore, the bimodal trend of clozapine plasma concentrations found in our study supports this latter assumption. It appears that a proportion of patients require a minimum level around 350 ng/ml, while others would require concentrations of around 650 ng/ml to achieve significant symptom reduction. A similar study[12] found higher clozapine plasma concentrations (above 1000 ng/ml) to be associated with better clinical response, however more adverse effects. The exact pharmacological mechanism by which clozapine exerts its clinical efficacy is still unknown. However, It was suggested previously[33,34] that clozapine, unlike other antipsychotic compounds, is associated with low D2 receptor occupancy, whereas 5HT2 receptors are fully antagonised at the same doses. Imaging studies[35] showed that at plasma concentrations of 350 ng/ml, the D2 receptor occupancy is calculated to be 54%, while at concentrations of 650 ng/ml, the occupancy is calculated to be 60%. The association of clinical efficacy with higher plasma concentrations in a subset of patients may suggest that in these patients, a higher D2 blockage level might be required to achieve a sufficient clinical response. We were unable to determine any differences between the groups in our sample; however, based on our sample, albeit a bit speculative and should be done with caution, upping clozapine towards a level of 650 ng/ml in nonresponders should be considered.

Few previous clinical trials have investigated the association of clozapine use and functional recovery in persons with treatment-resistant schizophrenia (TRS). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, clozapine was clinically superior to other antipsychotic medication but did not demonstrate a superior effect on Quality of Life Scale change scores at 6 and 12 months relative to patients treated with olanzapine, quetiapine or risperidone.[36] In a meta-analysis of eight studies,[16] clozapine had not been found to be superior to other antipsychotics for improvement of psychosocial function. In this study, there was no association between the clozapine level and the measured functional and occupational ability. However, clinical improvement was positively correlated with the functionality level. This may suggest that the effect on functional improvement is not direct and maybe mediated through symptomatic relief with clozapine

Our study is naturally limited by its retrospective and naturalistic design and lack of direct prospective assessments of patients' clinical status. The cohort, of individuals referred by secondary mental health care services to a tertiary unit due to their refractory nature, is atypical and likely to reflect a greater degree of treatment resistance than that seen in standard practice. Furthermore, dose of clozapine was determined based on clinical status but not fixed or randomised. Generally, high-dose group tends to include more subjects with nonresponse or poor response to drugs in a flexible dose-setting study. Moreover, our patients

have clozapine in one nocte dose or in divided doses, and the plasma levels are taken 12 h after the last dose to provide a trough level. This timing can vary in a very few patients who are difficult to bleed and may require the ward doctors to take blood, rather than the regular phlebotomists; this delay in sampling time may have implications for the clozapine concentrations measured. Finally, we have not determined patient's smoking status or explored the impact of drug–drug interactions on clozapine/norclozapine concentrations which could also be factors influencing plasma clozapine levels. In this small sample, we could not clarify the systematic effect of specific comedication on clinical outcome, although we have described this in our earlier paper[23] describing the impact of comedication on symptom profiles in a larger sample.

Conclusion

Our findings suggest that clozapine may have optimal clinical effect associated with concentrations around 350 ng/ml or higher concentrations (around 650 ng/ml). We were not able to detect predictors for low or high concentrations among our sample. It is therefore recommended, in people who do not achieve adequate response with 350-ng/ml concentrations of clozapine to increase the dose to gain plasma concentrations around 650 ng/ml. We observed that improvement in clinical status was associated with positive functional and occupational outcome. The relationship of norclozapine concentrations with outcomes may warrant further investigation.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement

This study followed the principles of the Helsinki Declaration. The study was approved by the Clinical Academic Group of South London and Maudsley National Health Service (NHS) Foundation Trust, UK (DTC/2021/124). The need for written, informed patient consent was waived because the study was retrospective and data were anonymised.

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