Full Title:
5 year retrospective follow-up of new cases of Charcot neuroarthropathy – a single centre experience

Short Title:
Outcomes after 5 years of follow up of newly diagnosed Charcot

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Abstract

Background:

Few data describe the natural history of Charcot Neuroarthropathy treated with a total contact plaster cast (TCC).

Methods:

A 5 year retrospective analysis of 50 patients presenting with an acute CN, Assessing time to clinical resolution into appropriate footwear and assessing if initial immobilisation device influenced resolution time.

Results:

During the study period 42 patients (84%) of patients went into remission, 2 died during their treatment, 4 had major amputations, in 2 patients treatment was ongoing. 36 patients were treated with combination offloading devices, 6 were treated with one modality only. Median time to resolution for patients initially treated with a TCC was not significantly shorter than for those treated with a removable below knee boot. 34.9% required re-casting due to clinical deterioration in the removable device.

Conclusions:

More precise measures of resolution of CN are needed to assess the impact of initial treatment modality on time to resolution.
Keywords
Charcot neuroarthropathy
Diabetes
Clinical resolution
Total contact plaster cast
Below knee removable walking boot
Introduction

Diabetes mellitus (DM) is a common condition affecting 382 million people globally, a number predicted to rise to 592 million by 2035 [1]. Diabetic foot disease is a common problem globally, and has major consequences for patients and society in general [2]. Between 2010 and 2011 the estimated cost of diabetes related ulceration and amputation to England was £639-661 million [3].

This data also showed that regular contact with a specialist diabetic foot multidisciplinary team decreased the costs to the NHS [3].

Charcot neuroarthropathy (CN) is an uncommon complication of diabetes. Population based studies have estimated a prevalence of CN of 0.1-0.5% in people with diabetes, rising to 13% in high risk patients [4]. Patients may present to any one of several different specialities such as orthopaedics, rheumatology or even accident and emergency departments. The diagnosis is frequently missed, and there is often a delay in starting treatment [5]. Once diagnosed, the treatment is immobilisation using a total contact plaster cast (TCC) or, if this is not available, a removable below knee walking boot [6]. It has been estimated that the average cost of managing a CN in community and outpatient setting is £2,710 per foot. The total cost for treating CN in the UK is over £6.5 million per annum [3].

Whilst uncommon, CN can be a potentially devastating end-stage complication of diabetes mellitus. If there is a delay in treatment, CN is often associated with
progressive foot deformity and resultant ulceration and infection. For patients with an uncomplicated CN, the risk of amputation is <2% [7]. However, the presence of an ulcer increases the risk of amputation between 12-13 times [7].

The pathogenesis of CN is presently poorly understood [6]. However, the longstanding theory regarding the pathophysiology of the disease - the neurotrophic theory originally described by Charcot, still has a role [8]. In addition, more recent work suggests that the inflammatory cascade plays an important role in developing the condition and may be a therapeutic target in the future [9].

A recent, large systematic review suggested that the current gold standard management of acute CN consists of immediate referral to a multidisciplinary foot-care team followed by immobilisation of the foot in a TCC [10]. These recommendations are consistent with the guidelines from the UK National Institute for Clinical and Health Care Excellence [11]. However, we acknowledge that there are variations in what people accept as the gold standard – with some centres using alternative methods of immobilisation such as the instant total contact cast or removable devices. A large prospective randomised trial is needed to address this.

There are few data describing the natural history of CN, particularly when treated with the TCC. A recent multicentre observational study of patients with acute CN
found that median time to resolution was 9 months in patients treated initially with a non-removable offloading device, compared to 12 months in those treated initially with a removable offloading device [12]. The same authors also reported a major amputation rate of 3.1% (n=9).

To further our understanding of the natural history of acute CN treated with TCC, we undertook a retrospective single centre study. Our aim was to look at time taken to achieve clinical resolution and to see if the initial device used to immobilise the foot influenced time to resolution. A secondary outcome was to see how many people relapsed when they came out of the TCC. A further secondary outcome was to see if the location of the Charcot influenced time to clinical resolution.
Methods

We performed a retrospective analysis of patients presenting to a single centre tertiary foot clinic with a diagnosis of acute CN between October 2007 and October 2012. Patients were searched our electronic database using the keyword “Charcot”.

Patients were included in the study if they had either type 1 or type 2 DM. The acute CN must have developed within the study period, and the patients must have been managed as an acute CN. Patients were excluded if an acute CN was deemed unlikely from the history and clinical examination, or if imaging studies were negative or another diagnosis was found to be causative or more likely. A strong clinical suspicion of acute CN with negative imaging studies would not exclude a patient from the study. Patients were also excluded if they had a chronic CN.

Data collection was achieved by the examination of electronic hospital records and hand-written clinic notes. Baseline demographics for study subjects were recorded, as were details of the acute CN. We looked at the site of CN, method of treatment, time in treatment method, and time to resolution. Resolution was determined by the point of transition from treatment to either own or hospital supplied footwear. Data was also collected on complications such as amputation and mortality. Patients were followed-up until the end of the study period.
For baseline demographics such as HbA1c and retinopathy, the most recent value recorded within a one year timeframe either side of the diagnosis was used. This timeframe was set as often tests were last or next performed at the patients’ diabetes annual review.

Site of CN was categorised into one of the following: forefoot; mid-foot; hind-foot and ankle; or mixed. A pre-defined classification criteria was not used as not all patients were diagnosed radiologically, leaving uncertainty around the exact location of the CN when it involved the hindfoot or ankle.

Data were analysed using SAS statistical software, version 9.3 (Marlow, Buckinghamshire, UK).
Results

50 patients were included. All patients had foot pulses palpable, and were insensate to 10g Semmes-Weinstein monofilament testing at the time of diagnosis of CN. However, 2 people died during the course of the study. Figure 1 shows the numbers at each stage of the patient inclusion / exclusion criteria. All were diagnosed and managed at the same centre within the time period of the study. The specialist foot clinic was run by 2 of the authors (CG and KD) as part of the multidisciplinary foot clinic, which included 2 orthopaedic surgeons specialising in foot and ankle surgery.

The mean age (±SD) at CN diagnosis was 62.5±11.7 years. 34 (68%) were male. 11 (22%) had T1DM. The median duration of diabetes (IQR) was 32.0 years (19.8, 38.0) for those with T1DM, and 15.0 years (4.5, 20.0) for those with T2DM. Mean HbA1C (±SD) was 65±20mmol/mol (8.1%), (T1DM 70±19mmol/mol [8.6±3.9%]; T2DM 64±20mmol/mol [8.0±4.0%]).

At diagnosis of acute CN 12 patients had chronic kidney disease (CKD) stage 0 or 1, 21 patients (42%) had CKD stage 2 and 17 patients (34%) had CKD stage 3-4. 9 patients had no evidence of retinopathy, 27 had a grading of R1 (background), with 10 of these having R1, M1 (background retinopathy and macular involvement), 3 had R2 (pre-proliferative disease) – one of these had macular disease (R2 M1), 8 had R3 (proliferative retinopathy), 3 with macular
disease (R3 M1). 1 patient was recorded as having retinopathy with no grade given. Retinopathy data was unavailable for 2 patients.

Of the 50 patients, only 15 were able to recall an episode of trauma to the affected foot within the preceding 12 months. During the study period, 4 patients had major amputations and 3 had minor amputations or debridement to the affected foot.

40 patients (80%) had a difference in foot temperature of >2°C at presentation, with the affected foot being warmer. There was no data available for 4 (8%) patients. 6 patients (12%) had foot temperature difference of <2°C at presentation, however all of these were diagnosed and managed as acute CN on clinical grounds, with 4 of the 6 having an acute CN confirmed radiologically. In total, 30 patients (60%) had a diagnosis of acute CN confirmed radiologically, by X-ray, MRI or both. The others were treated on clinical grounds because they had presented with a hot, swollen, and deformed insensate foot but in whom repeated imaging showed no abnormality. All patients were followed up radiologically.

Charcot site

During the study, 42 patients went into remission, with foot temperatures <2°C for greater than 6 weeks (3 consecutive visits to the foot clinic) and stable radiographic imaging. Of these 11.9% were in the forefoot, 64.3% in the mid-
foot, 19.1% in the hind-foot or ankle, with 4.8% in multiple sites. Median times to resolution for CN depending on location were not significant (p=0.3814), and are shown in Table 1.

**Offloading device (Figures 2a and 2b)**

36 of the 42 patients who went into remission (85.7%) were treated with both TCC and removable offloading device. The removable offloading device was used to wean the patients out of the TCC and into footwear. 25 (59.5%) were initially treated with a TCC, whilst the remaining 17 (40.5%) started in a removable offloading device. 6 patients were treated with one modality only – 1 patient was treated with TCC only, and the other 5 were treated with a removable offloading device only. For these 42 patients, median time to resolution was 51.5 weeks (IQR 37-68). Of this, a median of 26 weeks (IQR 12-39) was spent in TCC, with 18 weeks (IQR 13-31) being spent in a removable offloading device.

Median time to resolution for the 26 patients initially treated with a TCC was 48 weeks (95% CI: 42.4, 64.4) compared to the median time of 53 weeks (95% CI: 42.5, 64.4) for the 22 patients initially treated with removable offloading device (p = 0.7681, Appendix 1).

43 patients out of the initial 50 patients in the study used a TCC at some stage during their treatment. Having achieved clinical remission using our standard definition, they transferred from a TCC into a removable device. However, 15 of
these 43 (34.9%) relapsed and required re-casting due to clinical deterioration of the acute CN. The median time to resolution for these 15 patients was 68 weeks (95% CI: 53, 89) compared to the 32 patients who had no re-casting, who had a median time to resolution of 42.5 weeks (95% CI: 35, 48) (P<0.0001 log rank test). More work needs to be done to try and identify those who are at greatest risk of clinical deterioration or when the correct time to take the cast off. We used the standard clinical indicators of 3 consecutive clinical appointments at least 2 weeks apart with a temperature difference of less than 2 degrees Celsius with stable radiological appearances to diagnose resolution of the CN [6].

13 out of the initial 50 patients had an ulcer on the same foot as the acute CN at the start of treatment. Of these, 1 patient underwent below knee amputation whilst 12 went successfully into remission without further complication. In 3 patients the CN was diagnosed when they presented with avulsion fractures to the foot.

Whilst patients were in a cast, very few developed any complications as a result. All of these were minor - the most common being a rub. However, no patients changed their treatment as a consequence of these. In addition, our clinical protocols mean that patients have their cast changed weekly or every other week, but in addition, they have 'open access to the specialist foot clinic if they feel they have a problem with the cast.
Time to healing was not associated with the presence of chronic kidney disease, retinopathy, HbA1c or duration of diabetes (see Appendix 1).
Discussion

This study has shown that 50 patients presented to our tertiary specialist foot clinic with a new diagnosis of Charcot neuroarthropathy during a 5 year period. When treated, the median time to resolution and transfer to appropriate footwear was 1 year (52.25 weeks, IQR 25, 81). Our study also showed a 34.9% deterioration rate after coming out of TCC, and found that re-plastering was found to be associated with a significantly increased time to resolution (p<0.0001, log rank test). This implies that despite clinical resolution of the acute phase of the Charcot process (a temperature difference of <2°C for 3 consecutive visits, each at least 2 weeks apart)[6] and a ‘step down’ into the removable below knee walking boot, those patients were taken out of the TCC too early. Another possible explanation for this is that the patients were more mobile than they had been advised to be, thus causing a reactivation of the Charcot process. However, our data is consistent with previous work that showed relapse rates vary, between 12% and 33% [13,14,15,16].

Our data further show that the longer the TCC remained on, the greater the time to resolution, but also a lower chance of subsequent deterioration. This is in contrast to the work by Christensen et al who showed that the use of a removable offloading device as the sole treatment method of acute CN led to average treatment duration of approximately 5 months [16]. This is significantly
The current data take into account that our service covers a large, predominantly rural, geographical area and when patients are first diagnosed they have often driven to the clinic. Whilst we would prefer to offer them the gold standard treatment of the TCC at the time of diagnosis, we are aware of the significant negative impact this decision would have on their lives and so many opt to use the below knee removable walking boot for a few days until they arrange transport back to our clinic to go into a TCC. We analysed whether this initial treatment modality had an impact on overall time to resolution. It is likely that the non-statistically significant shorter time to resolution in those patients initially treated with a TCC is a reflection of the relatively small sample size.

Whilst there is general consensus that immobilisation of the foot is necessary to prevent progression in the acute Charcot foot, there is generally poor quality evidence to differentiate between a TCC and a removable below knee walking boot [10]. The results of the current study are in contrast to those reported by the CDUK group who found that median time to resolution varies greatly between those initially treated in a non-removable device, e.g. a TCC compared to removable offloading device (9 months and 12 months respectively) [12]. That study, however, used data from many centres across the UK and there was no standardisation on set point or definition of ‘resolution’. This could have impacted
the duration of treatment. The authors also acknowledged that their work “may have been influenced by selection bias” despite their efforts to include all patients diagnosed with acute CN from each centre [12]. This made it difficult to draw conclusions on true treatment times because it was unknown which patients were and were not included. However, worldwide there is a significant variation in the median period of immobilisation; in the UK observational work has reported durations of 9-12 months [12], whilst data from the USA and other European centres reported periods of immobilisation for only 4-6 months [17,18,19]. We acknowledge that some of this variation may be due to differences in the offloading devices and techniques. For example, some areas may use double-shelled orthosis adapted to the patient but removable and patellar tendon-adapted, or in the US where the use of ‘knee scooters’ may be more prevalent. To address some of this variation in care, a national casting course has been developed in the UK [20]. Our results also agree with previous data presented in abstract form only from another large centre in the UK who found the median duration of treatment for their patients to be 11 months [15].

As others have reported, our patients had several diabetes related comorbidities, including chronic kidney disease and retinopathy [21,22], suggesting that the development of CN and other microvascular disease may share a common pathway.
4 patients underwent below knee amputation (BKA) within the duration of the study. Of these, 1 patient had a neuropathic ulcer and the others had hindfoot Charcot’s with significant deformity at presentation. Of these, 2 declined to be put into a cast and deteriorated to a stage where their foot and ankle became unstable. All of the patients declined any reconstruction and their feet became unsalvageable. The final patient deteriorated despite being in a TCC for 34 weeks and developed significant ulceration and infection requiring amputation. Our study has shown an 8% amputation rate for patients with acute CN. Sohn et al suggested that the presence of an ulcer increased the likelihood of amputation 12 fold [7]. Our amputation rate was higher than found by several recent studies, with the UK wide CDUK group reporting a 3.1% major amputation rate, and the 2% reported by Sohn et al, but much lower than the rate reported by Gazis et al of 23.4% [12,7,23]. However, there remain concerns about the validity of their data because of the previously mentioned concerns – that the CDUK study had a degree of selection bias [12], and the data from Sohn et al also included data from several centres, and they too noted they were unable to obtain data on amputation rates from some centres, so their figures are likely to be an underestimate [7].

The mortality reported in the present study is in line with previous work. Armstrong et al reported no deaths among 55 patients during a 92.6 week mean follow-up [19], with Fabrin et al reporting a 1.7% mortality among 115 patients during a 4 year follow up [14]. In contrast, Jeffcoate et al. showed a mortality of
44.7% amongst 47 patients with a mean of 3.7 year follow-up and a major amputation rate of 1.7% [23]. A more recent study showed a lower mortality of 18.6% amongst 70 patients with CN after a median follow-up of 2.1 years, However, this was not statistically significantly different from the mortality rate amongst 66 matched control patients (p = 0.094) [24].

There are few robust data describing the influence of anatomical location and rates of healing. However, our data are in contrast to previous work from a smaller cohort, that suggested that the duration of immobilisation may be influenced in part by the anatomical location of the CN [17].

The strength of the current paper is that it is data from a single site with complete follow up on all of the patients. All of the patients were managed in the same way by the well-established diabetic foot MDT. Our team are able to offer our preferred initial treatment modality for Charcot, the TCC, in the diabetic foot clinic at the time of initial diagnosis, without delay.

It has recently been suggested that the findings on MRI should be adopted as the criterion standard for establishing disease activity and diagnosing remission [25]. This is because MRI has the greatest potential to monitor the effect of treatment since it shows bone marrow oedema. However, the use of serial MRI as a tool to monitor for signs of disease remission was not used in our centre because it was not routinely recommended and remains a tool to be kept in reserve as
suggested in a recent systematic review [10]. There is emerging data to suggest that this should change, and MRI should be used more frequently [26].

Limitations include that our population is exclusively White Caucasian, and thus the generalizability may be limited when considering other populations.

Furthermore, only 60% had a confirmed radiological diagnosis of a Charcot foot – with all of the others being radiologically normal, but with all of the other clinical features of a Charcot foot. The recommendations are to treat on clinical ground and not wait for radiological confirmation [10]. In addition, we feel that we have an excellent primary care network that refers to the specialist foot clinic early, thus preventing the development of bony deformity.

We were unable to determine compliance with minimal weight bearing and the use of removable offloading devices when they were issued. Previous work has shown that compliance levels are low when devices are removable [27]. Future work may be able to use newer technologies to assess this.

We are a tertiary referral centre, and over 15% of our work comes from other centres that are unable to apply a TCC. Patients are referred to us if there are no early signs of clinical resolution, usually in removable device. This is likely to lead to a longer time to resolution. Furthermore, there may have been a delay in the time between healing and the time for the patients to be provided with hospital footwear. During this time it was usual for patients to remain in the removable
device, thus artificially lengthening their time to resolution. However, this decision
to classify resolution until footwear was available was deliberate, and in line with
previous work [12], because for many patients this is the time that they are able
to return to their former levels of activity, and thus more accurately reflects the
personal impact of the disease on the patient.

In summary, this work has shown that initial treatment with a TCC improves
times to resolution for patients with acute CN. As a result of this work that all
patients referred to us with a suspected CN are advised on the telephone when
the appointment is being made, not to drive to their clinic appointment so that if a
cast needs to be applied, there is no delay.

However, a significant proportion of patients required re-immobilisation despite
using recognised markers of resolution. This study highlights the need to develop
more precise measures to help manage acute CN, and assess the impact of
initial treatment modality on time to resolution.


25. Chantelau EA, Richter A. The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging – a review of 71 cases. *Swiss Med Wkly* 2015;143:w13831-


Appendix 1
Summary of univariate results

Table 1
Time to improvement by site location in those 42 patients who went into remission.

Figure 1
Consort diagram to show patient selection process

Figure 2a
A picture of a total contact cast

Figure 2b
A picture of a below knee removable walking boot
## Table 1

<table>
<thead>
<tr>
<th>Time to Improvement By Site Location</th>
<th>N</th>
<th>N Missing</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>Median</th>
<th>IQ Range</th>
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<td>Active Charcot - forefoot</td>
<td>5</td>
<td>0</td>
<td>47.2</td>
<td>22.6</td>
<td>14</td>
<td>68</td>
<td>50</td>
<td>(37,67)</td>
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<td>Active Charcot – midfoot</td>
<td>27</td>
<td>2</td>
<td>56.2</td>
<td>30.3</td>
<td>16</td>
<td>159</td>
<td>53</td>
<td>(40,68)</td>
</tr>
<tr>
<td>Active Charcot – Ankle/hindfoot</td>
<td>8</td>
<td>4</td>
<td>51.8</td>
<td>23.1</td>
<td>12</td>
<td>79</td>
<td>53</td>
<td>(36.5,72)</td>
</tr>
<tr>
<td>Mixed</td>
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<td>0</td>
<td>53.0</td>
<td>39.6</td>
<td>25</td>
<td>81</td>
<td>53</td>
<td>(25,81)</td>
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</table>
Appendix 1. Summary of univariate results

Results for continuous variables

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<tr>
<th>Variable</th>
<th>Initial Device</th>
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<th>Mean</th>
<th>SD</th>
<th>N Missing</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>95% CI</th>
<th>IQ</th>
<th>Range(25th,75th)</th>
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<td>17</td>
<td>53.5</td>
<td>23.1</td>
<td>0</td>
<td>14</td>
<td>98</td>
<td>53.0</td>
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<td>(37.0,68.0)</td>
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<td></td>
<td>TCC</td>
<td>25</td>
<td>54.6</td>
<td>31.1</td>
<td>6</td>
<td>12</td>
<td>159</td>
<td>48.0</td>
<td>(42.4,66.8)</td>
<td>(38.0,67.0)</td>
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<tr>
<td>DM Duration</td>
<td>Removable</td>
<td>15</td>
<td>21.5</td>
<td>17.0</td>
<td>2</td>
<td>0</td>
<td>49</td>
<td>19.0</td>
<td>(12.9,30.1)</td>
<td>(6.0,35.0)</td>
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<td></td>
<td>TCC</td>
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<td>16.4</td>
<td>10.0</td>
<td>4</td>
<td>1</td>
<td>40</td>
<td>18.0</td>
<td>(12.7,20.2)</td>
<td>(8.0,23.0)</td>
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<td><strong>Age</strong></td>
<td>Removable</td>
<td>17</td>
<td>65.1</td>
<td>11.3</td>
<td>0</td>
<td>39</td>
<td>79</td>
<td>67.0</td>
<td>(59.8,70.5)</td>
<td>(57.0,73.0)</td>
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<td>60.5</td>
<td>12.0</td>
<td>0</td>
<td>43</td>
<td>82</td>
<td>61.0</td>
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<td>(49.0,70.0)</td>
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<td>17</td>
<td>63.2</td>
<td>17.6</td>
<td>0</td>
<td>37</td>
<td>101</td>
<td>61.0</td>
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<td>67.8</td>
<td>21.0</td>
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<td>42</td>
<td>115</td>
<td>61.0</td>
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<td>(52.0,85.0)</td>
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<td>41</td>
<td>7.0</td>
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<td>(1.0,14.0)</td>
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<tr>
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<td>TCC</td>
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<td>27.8</td>
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<td>0</td>
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<td>82</td>
<td>26.0</td>
<td>(21.0,34.5)</td>
<td>(15.0,35.0)</td>
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<td><strong>Second Device Duration</strong></td>
<td>Removable</td>
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<td>15.8</td>
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<td>0</td>
<td>55</td>
<td>8.0</td>
<td>(8.4,23.5)</td>
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<td>31</td>
<td>14.3</td>
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<td>0</td>
<td>74</td>
<td>13.0</td>
<td>(8.9,19.6)</td>
<td>(3.0,18.0)</td>
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<td><strong>Time in TCC</strong></td>
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<td>16</td>
<td>23.5</td>
<td>20.1</td>
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<td>0</td>
<td>57</td>
<td>21.5</td>
<td>(13.7,33.3)</td>
<td>(3.0,32.5)</td>
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<td>TCC</td>
<td>29</td>
<td>33</td>
<td>26.0</td>
<td>2</td>
<td>2</td>
<td>106</td>
<td>26.0</td>
<td>(23.6,42.5)</td>
<td>(15.0,47.0)</td>
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### Summary of univariate results

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Patients identified by hospital database search – keyword ‘Charcot’ (n=330)

Initial exclusions (n=251):
- Inappropriate referral letter (n=126)
- Other diagnosis (n=50)
- Unable to locate letter (n=14)
- Chronic CN (n=61)

Acute CN suspected (n=79)

Acute CN diagnosed (n=50)
- Died (n=2)
- Included in data analysis (n=48)

Suspected then excluded after history and examination (n=14)

Excluded (n=15):
- Ischaemic leg (n=3)
- Patient not T1DM/T2DM (n=2)
- CN managed elsewhere (n=2)
- Lost to follow up (n=3)
- Declined management (n=2)
- Notes unavailable (n=3)