# The diagnostic usefulness of the combined COMPASS 31 questionnaire and electrochemical skin conductance for diabetic cardiovascular autonomic neuropathy and diabetic polyneuropathy

**Running head**

COMPASS 31 and sudomotor function assessment

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**Abstract**

**Background and Aims.** The study investigated the diagnostic performance for diabetic cardiovascular autonomic neuropathy (CAN) and polyneuropathy (DPN) of the combined use of COMPASS 31, validated questionnaire for autonomic symptoms of CAN, and electrochemical skin conductance (ESC), proposed for detecting DPN and CAN.

**Methods.** One-hundred and two participants with diabetes (age 57±14 years, duration 17±13 years) completed the COMPASS 31 before assessing cardiovascular reflex tests (CARTs), neuropathic symptoms, signs, vibratory perception threshold (VPT), thermal thresholds (TT), and ESC using Sudoscan. Two patterns were evaluated: 1) the combined abnormalities in both tests (*COMPASS 31+ESC*), and 2) the abnormality in COMPASS 31 and/or ESC (*COMPASS 31 and/or ESC*).

**Results.** CAN (≥1 abnormal CART) and confirmed CAN (≥2 abnormal CARTs) were present in 28.1% and 12.5%, DPN (2 abnormalities among symptoms, signs, VPT and TT) in 52%, abnormal COMPASS 31 (total weighted score >16.44) in 48% and abnormal ESC (hands ESC <50 µS and/or feet ESC <70 µS) in 47.4%. Both the patterns - *COMPASS 31+ESC* and *COMPASS 31 and/or ESC* - were associated with CAN and DPN (P<0.01). COMPASS 31 and ESC reached a sensitivity of 75% and 83% for confirmed CAN, and a specificity of 65% and 67% for DPN. When combining the tests, the sensitivity for CAN rose by up to 100% for CAN and the specificity up to 89% for DPN.

**Interpretation.** The combination of the tests can allow a stepwise screening strategy for CAN, by suggesting CAN absence with combined normality, and prompting to CARTs with combined abnormality.

**Key words**

Diabetes, diagnosis, neuropathy, symptoms, sudomotor function

## Introduction

Cardiovascular reflex tests (CARTs) are still the gold standard for the diagnosis of cardiovascular autonomic neuropathy (CAN) (1, 2). However, universal screening and the diagnosis of CAN are widely disregarded in clinical practice. This dichotomy between the ideal and actual reality highlights the need for diagnostic procedures of sufficient reliability and accuracy that are at the same time accessible and easy, and that might also at least allow for the selection of persons at higher risk for CAN and then candidates to CARTs.

The assessment of autonomic symptoms is recommended in guidelines (2, 3), however, this evaluation had been considered of poor diagnostic utility given their low specificity and the unavailability of easy-to-use validated questionnaires. Composite Autonomic Symptom Score (COMPASS) 31 was developed from COMPASS, which in turn had been derived from the Autonomic Symptom Profile (ASP), by cutting the number of items from 169 to 31 questions (4-6). The COMPASS 31 questionnaire has been translated into Italian and validated according to standard procedures by Pierangeli et al (7). Using this Italian version, we validated COMPASS 31 for autonomic symptoms of diabetic neuropathy and found a fair diagnostic accuracy for both CAN and diabetic polyneuropathy (DPN) with areas under the ROC curve of 0.75 and 0.74, respectively, and values of sensitivity up to 75% for CAN and of specificity up to 79% for DPN (8). COMPASS 31 had the additional advantage of being easy to use, inexpensive and of clinical relevance for patients.

Quantitative assessment of sudomotor function has been widely considered as a key component of the diagnostic pathway of autonomic and small fibre neuropathies (1, 9, 10), and many testing modalities are available. With most of them, however, being complex and highly demanding from a technical and setting perspective, their use has thus been limited to specialized laboratories (11). Among those of lower complexity, in recent years electrochemical skin conductance (ESC) measurement using Sudoscan has been proposed as a reliable and easy-to-use device for sudomotor function assessment mainly in diabetic neuropathies (12-14). There is however some uncertainty about the actual meaning of ESC values: at one extreme ESC measurements and in particular an algorithm derived risk score based on both ESC results and clinical parameters are proposed as a

panacea index able to predict both diabetes itself and diabetic complications, while at the other extreme the physiological justification of ESC as a measure of sudomotor function or just of sweat glands is questioned (11, 15-16). The question of whether reduced ESC is the consequence of sudomotor fibre loss, reduced numbers or volume of sweat glands or sweat gland dysfunction (11, 15) remains open. Moreover, when considering studies attempting to validate ESC measurement for the diagnosis of diabetic neuropathy, while values of sensitivity from 20% to 97% and specificity from 55% to 96% have been reported for DPN (13, 14, 17-24), data on diagnostic performance of ESC for CAN are limited (14, 25, 26), and characterised by various diagnostic modalities for the number of CARTs used (from 2 to 4), an inconsistent use of age-related normative values for CARTs, and the substitution of feet or hands ESC measures for a scoring measure called CAN risk score based on both ESC results and clinical parameters (25, 26) (Table 1).

The ease of COMPASS 31 and ESC might represent an opportunity to obtain a screening modality for CAN and the identification of candidates for CARTs performance. Thus, this cross-sectional clinic-based study is aimed at investigating the diagnostic utility of the combined use of COMPASS 31 and ESC, by evaluating the diagnostic performance for CAN of the abnormality in both COMPASS 31 and ESC (*COMPASS 31+ESC*), and of the abnormality in COMPASS 31 and/or ESC (*COMPASS 31 and/or ESC*) in a well-characterized diabetic population and using a comprehensive neurological examination. A secondary objective was to investigate the diagnostic performance for DPN of abnormalities in *COMPASS 31+ESC and COMPASS 31 and/or ESC.*

## Materials and Methods

*Patients*

From November 2016 to July 2017, we evaluated 125 consecutive outpatients at the secondary care diabetic clinic of the University Hospital of Rome Tor Vergata, Italy. Criteria for inclusion were the diagnosis of Type 1 or Type 2 diabetes, and age between 18 and 80 years. Exclusion criteria were severe comorbidities (eGFR <45ml/min, recent cardiovascular events, heart failure), peripheral or autonomic neuropathies from other causes than diabetes, advanced peripheral arterial disease, active limb ulcers, conditions precluding comprehension of the questionnaires like psychiatric disorders, and the presence of a cardiac pacemaker.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki as revised in 2013 and was approved by the Ethics Committee of the University Hospital of Rome Tor Vergata. All participants gave their written informed consent prior to inclusion in the study.

A complete clinical history regarding diabetes, its complications and comorbidities, and the ongoing treatments in particular with drugs interfering with CARTs (like furosemide, alpha-lytic or psychoactive agents) was collected. Anthropometric variables, including height, weight, waist circumference, and casual blood pressure were measured. Routine laboratory assessment including HbA1c, lipid profile, serum creatinine, and microalbuminuria, and ophthalmoscopic examination were carried out.

*Autonomic neuropathy assessment*

Participants were requested to complete COMPASS 31 in its Italian version before undergoing the other examinations. According to our previous studies of validation of COMPASS 31 for autonomic symptoms of diabetic neuropathy, COMPASS 31 was considered abnormal in the presence of a Total Weighted Score (TWS) >16.44 (8, 27). Operators were blinded to the COMPASS 31 results.

Four CARTs, three based on heart rate variation (deep breathing, lying to standing, Valsalva manoeuvre), and orthostatic hypotension test were performed using age-related reference values for heart rate based CARTs (28). An autonomic score was derived from CARTs results as an index of overall CAN severity by giving a score of 0 to a normal result, 1 to a borderline result and 2 to an abnormal result. We considered participants with ≥1 abnormal cardiovagal test as having CAN and those with ≥2 abnormalities as having confirmed CAN (2, 29).

*DPN assessment*

Neuropathic symptoms and deficits related to DPN were evaluated using the Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q), and the Michigan Diabetic Neuropathy Score (MDNS) (30). Moreover, vibration perception threshold (VPT) was measured using Biothesiometer at the hallux dorsum and at the lateral malleolus (31); age-related normal values derived from literature were used (32). Warm (WTT) and cold thermal perception thresholds (CTT) were assessed with TSA-II Neurosensory Analyzer (Medoc, Ramat Yishai, Israel) at the dorsum of both feet following the level test procedure (33). Criterion for the definition of DPN (probable) was the presence of at least two abnormalities among symptoms, signs, VPT and thermal perception thresholds (29).

*Sudomotor function assessment*

Sudomotor function was assessed by an operator unaware of the neurological assessment through ESC measured at the hands and feet using Sudoscan (Impeto Medical, Paris, France). ESC is based on an electrochemical reaction between sweat chloride and stainless steel electrodes in response to applied low voltage direct current (34), thus it reflects the flow of chloride ions from sweat glands to the skin caused by an electric current through the activation of the sympathetic sudomotor fibers or a direct stimulation of sweat glands (15, 35). Participants were requested to avoid previous

application of moisturizing creams, and instructed to put both palms and both feet simultaneously on electrodes. ESC results were considered abnormal if <50 µS and <70 µS for hands and feet respectively (34, 36).

*Statistical analysis*

Considering the results obtained with COMPASS 31 and ESC feet in the previous studies in participants with DPN or CAN (8, 14, 20), a sample size of ~90 was planned.

Data are expressed as mean ± standard deviation (SD). Student's *t*-test as test of significance for means, the Chi square test for categorical variables, and Spearman coefficients for relationships were used. A value of P <0.05 was considered significant. Fisher's exact P value was considered for Chi square test. Analysis of covariance was used to compare the continuous variables of major interest, i.e. COMPASS 31 TWS and ESC, between groups with and without CAN and DPN taking into account those clinical variables possibly related to COMPASS 31 TWS and ESC (37).

The diagnostic accuracy of isolated COMPASS 31 and ESC measurement for CAN and DPN was assessed through the area under the receiver operating characteristic curve (AUC), as well as the sensitivity, specificity, positive and negative predictive value, and the likelihood ratios for the combination of abnormalities of *COMPASS 31+ESC and COMPASS 31 and/or ESC*. Two-sided 95% confidence intervals (C. I.) were also calculated. All statistical analyses were done using STATA (StataCorp LP, College Station, TX, USA).

## Results

According to the selection criteria, 102 subjects, 63 males and 39 females, all white, were included in the study. Table 2 describes the clinical characteristics of the studied population. Mean age and duration of diabetes were 57 years and 17 years, 66 (64.7%) had type 2 diabetes.

CARTs were not successfully performed in 6 participants due to technical reasons like the presence of irregular rhythm and artefacts on ECG recording during testing. These 6 patients were not classified with regard to CAN and therefore not included in the statistical analysis concerning CAN. Thus, among the 96 subjects with CAN assessment, confirmed CAN and CAN (both early and confirmed) were present in 12 and 27 (12.5% and 28.1%, respectively).

In the whole studied population, DPN was present in 51.9%, abnormal COMPASS 31 in 47.4% and abnormal ESC (hands and/or feet) in 48.0% (Table 2).

Mean COMPASS 31 TWS was significantly higher in patients with confirmed CAN compared to those without (P=0.0025), and in those with DPN compared to those without (P=0.0017) (Table 3). COMPASS 31 TWS was related to autonomic score (rho=0.209, P=0.0487), deep breathing (rho=-0.285, P=0.0072), lying to standing (rho=-0.212, P=0.0470), mean VPT hallux (rho=0.254, P=0.0139), MDNS (rho=0.345, P=0.0008), MNSI-Q (rho=0.583, P<0.0001), WTT (rho=0.281, P=0.0091), and CTT (rho=-0.294, P=0.0064). On the other hand, COMPASS 31 TWS was not related to any of clinical variables as age, sex, BMI, diabetes duration, HbA1c and lipids.

Mean values of ESC significantly differed according to the presence of CAN (P <0.0001) and DPN (P=0.0004 for ESC hands and P <0.0001for ESC feet) (Table 3). The only relationship between ESC and clinical variables was that of mean ESC feet with triglycerides (rho=-0.273, P=0.0065). In the analysis of covariance after adjustment for triglycerides, the significant differences in mean ESC feet between the groups with and without CAN and with and without DPN retained the same degree (P<0.0001). Moreover, mean ESC feet was related to autonomic score (rho=-0.381, P=0.0002), deep breathing (rho=0.543, P<0.0001), lying to standing (rho=0.343, P=0.0009), Valsalva ratio (rho=0.379, P=0.0012), VPT hallux (rho=-0.302, P=0.0024), MDNS (rho=-0.368, P=0.0002), and MNSI-Q (rho=-0.221, P=0.0267). Mean ESC hands showed similar correlations with autonomic score (rho=-0.256, P=0.0126), deep breathing (rho=0.415, P<0.0001), lying to standing (rho=0.428, P<0.0001), Valsalva ratio (rho=0.265, P=0.0238), VPT hallux (rho=-0.266, P=0.0075), and MDNS (rho=-0.227, P=0.0223).

No association was found between abnormality in ESC and COMPASS TWS, as well as no correlations between ESC and COMPASS 31 scores, apart from that between hands ESC and vasomotor domain score (rho=0.229, P=0.246).

Two patterns of abnormalities of COMPASS 31 and ESC, i.e. *COMPASS 31+ESC* and *COMPASS 31 and/or ESC*, were more frequent in participants with CAN ($Chi^2$=7.57, P=0.0088 and $Chi^2$=8.20, P=0.0045), confirmed CAN ($Chi^2$=7.44, P=0.0118 and $Chi^2$=5.73, P=0.0159), and DPN ($Chi^2$=9.04,

P=0.0041 and $Chi^2$=9.04, P=0.0041), compared to those without (Fig. 1). In particular, the totality of participants with confirmed CAN had the pattern *COMPASS 31 and/or ESC*.

When considering the diagnostic accuracy of tests using ROC analysis, COMPASS 31 TWS showed values of AUC of 0.62 for the diagnosis of CAN, 0.73 for confirmed CAN and 0.68 for DPN (Fig. 2). Moreover, values of AUC of ESC feet were 0.74, 0.92, and 0.69 for the diagnosis of CAN, confirmed CAN and DPN, respectively (Fig. 3). Moreover, at the cut-off of 16.44, COMPASS 31 TWS reached a sensitivity of 75% for confirmed CAN, whereas the abnormality of ESC hands and/or feet had a value of sensitivity of 83% (Table 4). When combining the tests, the diagnostic performance of the two patterns of abnormalities *COMPASS 31+ESC* and *COMPASS 31 and/or ESC* rose by up to 100% for the sensitivity for CAN and 89% for the specificity for DPN (Table 5).

## Discussion

*COMPASS 31 results*

Recently, we validated COMPASS 31 for autonomic symptoms of diabetic autonomic neuropathy (8). In the validation study, in 73 participants with diabetes, we observed that COMPASS 31 scores were associated with CAN and DPN, related to their severity, and that COMPASS 31 TWS had a fair diagnostic accuracy for CAN and DPN with AUCs of 0.75 for CAN and 0.74 for DPN, and sensitivity and specificity of 75% and 65.5% for CAN and of 65.5% and 79.5% for DPN (8). Moreover, COMPASS 31 had good internal consistency with a Cronbach's coefficient of 0.73 (8).

Therefore, the diagnostic performance of COMPASS 31 proved to be better than expected on the basis of the assumption of a relatively low specificity and also the late appearance of symptoms in the natural history of diabetic autonomic neuropathy. Based on these findings, COMPASS 31 was proposed as a quantitative assessment tool for autonomic symptoms in diabetic neuropathy, possibly useable as a screening tool in clinical practice. The Survey of Autonomic Symptoms had been also validated for the diagnosis of diabetic neuropathy and suggested as a valid and easily administered tool for autonomic symptoms in early diabetic neuropathy, given that the studied population included almost exclusively subjects with impaired glucose tolerance (94%) (38).

In the present study COMPASS 31 would appear to retain similar characteristics of diagnostic performance for CAN and DPN, with values of AUC up to 0.73, sensitivity up to 75% and specificity up to 65%, but with values for DPN being slightly lower than in the previous study. This may be due to differences between the populations of the present and previous study (8) like a larger sample size (102 Vs. 73), a longer diabetes duration (18 Vs. 12 years), and a higher prevalence of DPN (52% Vs. 40%). However, an AUC of 0.73 for confirmed CAN supports overall fair diagnostic accuracy of COMPASS 31 (a value >0.7). The associations of higher values of COMPASS TWS with the presence of CAN and DPN and its relationship with most neurological measures of small and large fiber function confirm our previous reports (8).

*ESC results*

With regard to sudomotor assessment, we found that hands and feet ESC were lower in participants with CAN and DPN and were significantly related to all cardiovascular tests (in particular with deep breathing test: $P<0.0001$) and the autonomic score, to the scores of neuropathic symptoms and

signs, and to VPT, but not to thermal thresholds. These findings confirm previous observations (13, 14, 19) of correlations of hands and feet ESC with clinical neuropathy scores (i.e., NIS-LL, UENS and MNSI, NDS and NSS, TCNS) (13, 19, 22, 39-41), deep breathing (13, 14), Valsalva test (13), CARTs based autonomic score (14), VPT (14, 20, 21, 41), and thermal thresholds, with the lowest significance for the latter (13). In the current study, feet ESC showed a fair diagnostic accuracy for CAN, in particular for confirmed CAN with an AUC of 0.92, while the abnormality of hands or feet ESC had the best sensitivity for confirmed CAN (83%) and the best specificity for DPN (67%). The values of sensitivity for CAN position themselves intermediately between the lower ones of Selvarayah et al (14) and the higher ones of Yainjk et al (25) and Yuan et al (26), who used, however, a composite score based on ESC and clinical variables. With regard to DPN, when considering studies with a diagnosis of at least probable DPN (13, 14, 17, 19, 20, 22, 40), the sensitivity of 62% found here was lower than previously observed, ranging from 67.5% to 87.5%, and the specificity of 67% in the middle of the range from 53% to 92% (Table 1).

*Combination of COMPASS 31 and ESC*

This study was aimed at answering the question of whether the combination of COMPASS 31 and ESC works better than the single tests. We explored two patterns: the presence of both abnormalities and the presence of at least one abnormality among COMPASS 31 and ESC. The study found that sensitivity and specificity improved when using the tests in combination, in particular for CAN, with a sensitivity of 92% for CAN and 100% for confirmed CAN with the pattern of *COMPASS 31+ESC*, and a specificity of 82% and 79% for CAN and confirmed CAN with the pattern *COMPASS 31 and/or ESC*. Diagnostic performance improved also for DPN with a sensitivity of 85% and a specificity of 89% with two patterns respectively.

The diagnostic value for DPN of these autonomic tests deserves some comments. While the ability of ESC to discriminate the presence of DPN is more obvious, given the distal localization of sweat glands, the presence of vasomotor and secretomotor domains in the COMPASS 31, exploring symptoms related to skin color and sweating changes might explain the association with DPN, although no preferential relationship between these domains and DPN was found in the previous work (8), like in the present study. It is noteworthy that ESC was not associated with COMPASS 31

results, apart from the correlation between hand ESC and vasomotor domain score. The lack of association between ESC and COMPASS 31 was also observed in 82 symptomatic subjects with hATTR V30M amyloidosis (42). The absence of overlapping between abnormalities in COMPASS 31 and ESC might contribute to the better diagnostic performance of their combination.

COMPASS 31 is an easy-to-use, time-saving and inexpensive tool, useable as a self-questionnaire in the waiting room, which addresses the need to evaluate autonomic symptoms and also works as a screening tool for CAN and DPN. ESC measurement is easy to perform, of very short duration, does not require complex subject cooperation (apart from the need to maintain one's palms stable on the electrodes) or special training for personnel, but it does require an expensive device. This study for the first time documents that the combination of the two procedures improves the performances obtained when used separately. Moreover, the lack of associations between COMPASS 31 and ESC results suggests that they explore distinct abnormalities and might complement each other.

*Strengths and limitations*

The strengths of this study are the well-characterized diabetic population, the use of gold-standard tests for CAN diagnosis and a multilevel diagnostic approach to DPN including symptoms, signs, VPT and thermal thresholds to reach the diagnosis of *probable* DPN (29). A limitation is the lack of a nerve conduction study or skin biopsy to get a confirmed diagnosis of DPN (29). Moreover, we did not use normal reference values for ESC provided by our laboratory but those available from literature. Participants did not withdraw diuretics or alpha-lytics, the drugs that interfere most with CARTs, before testing. However, the associations of CAN and DPN with COMPASS 31 and ESC did not change after adjustment for the use of these agents in the analysis of covariance.

There is some debate on the meaning of ESC in the scenario of sudomotor function assessment. Given that ESC measures the amount of sweating in response to current, it can represent the number of preserved sweat glands more than the efficiency of autonomic pathways and fibres. It is not in the remit of this study to disentangle this aspect or to delineate whether the impaired ESC is a surrogate marker for a general state of patients with diabetes or effectively the expression of damaged or dysfunctional neural pathways controlling sudomotor function. The study documents

that ESC is associated with the presence of CAN and DPN and is related to the degree of impairment of neurological measures. Previous studies, using the gold-standard for sudomotor function QSART, have shown weak correlations between sweat volume of lower limb and feet ESC (19, 22), and recent reviews have described in detail the differences between these techniques assessing sudomotor function (11, 15, 35). Thus, the use of ESC as a marker of distal autonomic function seems to be supported although a conclusive demonstration of its direct assessment of sudomotor function is lacking. Moreover, correlations between ESC and morphology of small fibres have been reported by some authors using skin biopsy parameters although weaker than expected (15, 19, 43) and denied by others using corneal confocal microscopy measures (44). Finally, ESC has been advocated as a sensitive outcome in an intervention study with bariatric surgery in subjects with prediabetes and type 2 diabetes (45), but also the associations between ESC and CARTs were inconsistent at 1-year follow-up in 37 subjects with type 1 diabetes and free of complications, and the ESC decline unrelated to clinical variables and standard autonomic measures (46). The position statement of the American Diabetes Association did not recommend routine screening for sudomotor dysfunction in clinical practice (3).

*Conclusions*

This study documents that the combination of COMPASS 31 and ESC is able to provide a better diagnostic performance for CAN and to a lower degree also for DPN, reaching a high level of sensitivity with the pattern of an abnormality in the results of either COMPASS 31 or ESC and of specificity with the pattern of abnormalities of both tests. Although for all techniques that assess different outcomes from autonomic cardiovascular function the statement that they cannot replace established CARTs is still reasonable, in a busy clinical setting, the combination of these two simple and time-saving tests can allow a stepwise screening strategy for CAN, by suggesting with high probability the absence of disease in the case of combined normality, and prompting to standard CARTs in the case of combined abnormality in COMPASS 31 and ESC. However, given the low PPV and the limited ability of the combined abnormality to predict the presence of CAN, CARTs are still needed to get a final diagnosis.

The limited sample size of this study requires further validation in a larger, possibly multi-center, population with diabetes.



**Prior Presentation.**

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**Disclosure**

The Authors declare that there are no potential conflicts of interest relevant to the subject of this study.



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Table 1. Sensitivity and specificity of Feet ESC for CAN and DPN in the available published studies.

| Author, year (country) | Diabetic Population | CAN measures | CAN | | DPN measures | DPN | |
|---|---|---|---|---|---|---|---|
| | | | Sensitivity | Specificity | | Sensitivity | Specificity |
| Yajnik, 2012 (India) (17) | 265 type 2 | - | - | - | Symptoms, Signs, QST | 73 | 62 |
| Casellini, 2013 (US) (13) | 20 type 1<br>63 type 2 | - | - | - | Symptoms, Signs, QST | 78.3 | 92.4 |
| Yajnik, 2013 (India) (25) | 232 type 2 | DB, LS | 92 (CAN-RS 35%) | 49 (CAN-RS 35%) | - | - | - |
| Eranki, 2013 (India) (18) | 309 type 2 | - | - | - | QST | 82 | 55 |
| Smith, 2014 (US) (19) | 22 | - | - | - | Symptoms, Signs, QST, NCS, IENFD | 77 | 67 |
| Selvarajah, 2015 (UK) (14) | 45 type 1 | HR, DB, LS, VR, OH | 60 | 76 | Symptoms, Signs, QST, NCS | 87.5 | 76.2 |
| Sheshah, 2016 (Saudi Arabia) (20) | 24 type 1<br>272 type 2 | - | - | - | Symptoms (NSS), Signs (NDS), QST (VPT), NCS: confirmed DPN | 67.5 | 58.9 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Goel, 2017 (India) (21) | 523 type 2 | - | - | - | Symptoms (DNS≥1)<br>VPT>15 V | 52<br>72 | 60<br>90 |
| Yuan, 2018 (China) (26) | 9 type 1<br>94 type 2 | DB, LS, VR | 98.5 (CAN-RS 20.5%) | 29.5 (CAN-RS 20.5%) | - | - | - |
| Binns-Hall, 2018 (UK) (39) | 5 type 1<br>231 type 2 | - | - | - | Symptoms and signs (TCNS) (ESC feet cut-off of 58.5) | 77.4 | 68.3 |
| Krieger, 2019 (Germany) (22) | 47 type 2 | - | - | - | Symptoms (NSS)<br>Signs (NDS)<br>NCS | 70 | 53 |
| Carbajal-Ramirez, 2019 (Mexico) (23) | 221 type 2 | - | - | - | Signs (MNSI) | 97 | Not provided |
| Cabré, 2019 (Spain) (24) | 100 type 2 | - | - | - | NCS | 20 | 96 |

CAN-RS: CAN risk score, based on both ESC results and clinical parameters; CARTs: Cardiovascular Autonomic Reflex Tests; DB: Deep Breathing test; DNS: Diabetic Neuropathy Symptom; IENFD: Intraepidermal Nerve Fiber Density; HR: Heart Rate; LS: Lying to Standing test; MNSI: Michigan Neuropathy Screening Instrument; NCS: Nerve Conduction Study; NDS: Neuropathy Disability Score; NSS: Neuropathy Symptom Score; OH: Orthostatic Hypotension test; QST: Quantitative Sensory Testing; TCNS: Toronto Clinical Neuropathy Score; VPT: Vibration Perception Threshold; VR: Valsalva Ratio

Table 2. Anthropometric, clinical, metabolic and neurological characteristics of 102 participants with diabetes. CARTs and CAN diagnosis are provided for 96 participants (see the text).

| Anthropometric characteristics | |
|---|---|
| Males/females | 63 : 39 |
| Age (years) | 57.13 ± 13.66 |
| BMI (Kg/m²) | 27.10 ± 4.34 |
| Clinical and metabolic characteristics | |
| Diabetes duration (years) | 17.48 ± 13.59 |
| Type 2 diabetes (%) | 64.7 |
| HbA1c (mmol/mol) | 54.5 ± 11.84 |
| Total cholesterol (mg/dl) | 169.27 ± 41.09 |
| Triglycerides (mg/dl) | 112.13 ± 54.40 |
| Retinopathy (%) | 37.9 |

| | |
|---|---|
| Microalbuminuria (%) | 15.6 |
| eGFR (ml/min x 1.73 $m^2$) | 86.32 ± 20.74 |
| Casual PA (mmHg) | 131.03/75.08 ± 17.07/10.01 |
| Hypertension (%) | 63.7 |
| Cardiovascular disease (%) | 26.5 |
| Peripheral vascular disease (%) | 12.1 |
| Alcohol consumption (%) | 35.0 |
| Current smokers (%) | 22.8 |
| Regular physical activity (%) | 44.3 |
| Neurological characteristics | |
| MNSI-Q | 2.29 ± 2.66 |
| MDNS | 4.54 ± 3.55 |
| VPT hallux (Volt) | 24.25 ± 13.83 |
| CTT dorsal foot (°C) | 28.69 ± 4.85 |
| WTT dorsal foot (°C) | 35.88 ± 4.01 |
| DPN (%) | 51.9 |
| Expiration/Inspiration Ratio | 1.26 ± 0.18 |
| Lying to Standing ratio | 1.16 ± 0.15 |
| Valsalva Ratio | 1.53 ± 0.30 |
| Orthostatic Hypotension (mmHg) | 12.22 ± 9.78 |
| Autonomic score | 1.40 ± 1.83 |
| CAN (%) | 28.1 |
| Confirmed CAN (%) | 12.5 |
| COMPASS 31 TWS | 20.34 ± 16.83 |
| Abnormal Compass 31 TWS (%) | 47.4 |
| ESC hands (µS) | 66.72 ± 16.52 |
| ESC feet (µS) | 69.28 ± 17.59 |
| Abnormal hands and/or feet ESC (%) | 48.0 |

CTT: Cold Thermal Threshold; MDNS: Michigan Diabetic Neuropathy Score; MNSI: Michigan Neuropathy Screening Instrument; VPT: Vibration Perception Threshold; TWS: Total Weighted Score; WTT: Warm Thermal Threshold

Table 3. Mean values of COMPASS 31 Total Weighted Score (TWS) and ESC hands and feet in patients with and without CAN (early and confirmed), confirmed CAN and DPN.

| | With CAN | Without CAN | P | With confirmed CAN | Without confirmed CAN | P | With DPN | Without DPN | P |
|---|---|---|---|---|---|---|---|---|---|
| COMPASS 31 TWS | 25.9 ± 19.4 | 18.3 ± 15.5 | 0.0530 | 34.1 ± 21.4 | 18.4 ± 15.3 | 0.0025 | 25.4 ± 18.3 | 14.7 ± 13.1 | 0.0017 |
| ESC hands (μS) | 55.1 ± 21.9 | 71.4 ± 11.7 | <0.0001 | 49.6 ± 21.5 | 69.3 ± 14.6 | <0.0001 | 61.3 ± 19.6 | 72.6 ± 9.6 | 0.0004 |
| ESC feet (μS) | 54.3 ± 23.5 | 74.9 ± 10.7 | <0.0001 | 41.6 ± 23.0 | 73.0 ± 13.0 | <0.0001 | 62.8 ± 21.1 | 76.3 ± 8.5 | <0.0001 |

Table 4. Diagnostic characteristics for CAN, confirmed CAN and DPN of abnormality in COMPASS 31 or ESC (hands and/or feet): sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictor Value (NPV), Likelihood ratio for positive (LR+) and negative (LR-) results. 95% CI in the brackets.

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR- |
|---|---|---|---|---|---|---|
| CAN | | | | | | |
| Compass 31 | 58 (39-77) | 56 (44-68) | 34 (20-48) | 77 (65-89) | 1.31 (0.86-2.01) | 0.75 (0.46-1.24) |
| ESC hands/feet | 78 (62-93) | 64 (52-75) | 46 (31-60) | 88 (79-97) | 2.15 (1.48-3.11) | 0.35 (0.17-0.72) |
| Confirmed CAN | | | | | | |
| Compass 31 | 75 (50-99) | 56 (45-67) | 20 (8-32) | 94 (87-100) | 1.71 (1.14-2.58) | 0.44 (0.16-1.21) |
| ESC hands/feet | 83 (62-104) | 57 (46-68) | 22 (10-34) | 96 (91-101) | 1.94 (1.36-2.77) | 0.29 (0.08-1.05) |
| DPN | | | | | | |
| Compass 31 | 59 (45-72) | 65 (51-79) | 65 (51-79) | 59 (45-72) | 1.69 (1.07-2.67) | 0.63 (0.43-0.93) |
| ESC hands/feet | 62 (49-75) | 67 (54-80) | 67 (54-80) | 62 (49-75) | 1.91 (1.21-3.00) | 0.56 (0.38-0-83) |

Table 5. Diagnostic characteristics for CAN, confirmed CAN and DPN of pattern *COMPASS 31+ESC* or *Compass 31 and/or ESC*: sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictor Value (NPV), Likelihood ratio for positive (LR+) and negative (LR-) results. 95% CI in the brackets.

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR- |
|---|---|---|---|---|---|---|
| CAN | | | | | | |
| *Compass 31+ESC* | 46 (27-65) | 82 (72-89) | 50 (30-70) | 79 (70-89) | 2.54 (1.31-4.90) | 0.65 (0.41- 0.96) |
| *Compass 31 and/or ESC* | 92 (82-103) | 38 (26-50) | 37 (25-49) | 93 (83-102) | 1.49 (1.19-1.85) | 0.20 (0.05-0.80) |
| Confirmed CAN | | | | | | |
| *Compass 31+ESC* | 58 (30-86) | 79 (70-88) | 29 (11-47) | 93 (86-99) | 2.74 (1.45-5.19) | 0.53 (0.27- 1.04) |
| *Compass 31 and/or ESC* | 100 (100-100) | 34 (23-44) | 18 (9-28) | 100 (100-100) | 1.51 (1.29-1.76) | 0 (0 - NaN) |
| DPN | | | | | | |
| *Compass 31+ESC* | 37 (24-50) | 89 (80-98) | 79 (63-95) | 56 (45-67) | 3.43 (1.39-8.43) | 0.70 (0.56- 0.89) |
| *Compass 31 and/or ESC* | 85 (75-94) | 44 (29-58) | 63 (51-74) | 71 (55-88) | 1.50 (1.13-1.98) | 0.35 (0.17-0.72) |

**Figure Legends**

Figure 1. Percentage of pattern *COMPASS 31+ESC* (abnormality in both measures) and pattern *COMPASS 31 and/or ESC* (abnormality in at least one measure) in patients with CAN, confirmed CAN and DPN.

Figure 2. Area under the Receiver Operating Characteristic (ROC) curve (AUC) of COMPASS 31 Total Weighted Score (TWS) for CAN and DPN.

Figure 3. Area under the Receiver Operating Characteristic (ROC) curve (AUC) of ESC feet for CAN and DPN.

Figure 1. Percentage of pattern *COMPASS 31+ESC* and pattern *COMPASS 31 and/or ESC* in patients with and without CAN, confirmed CAN and DPN

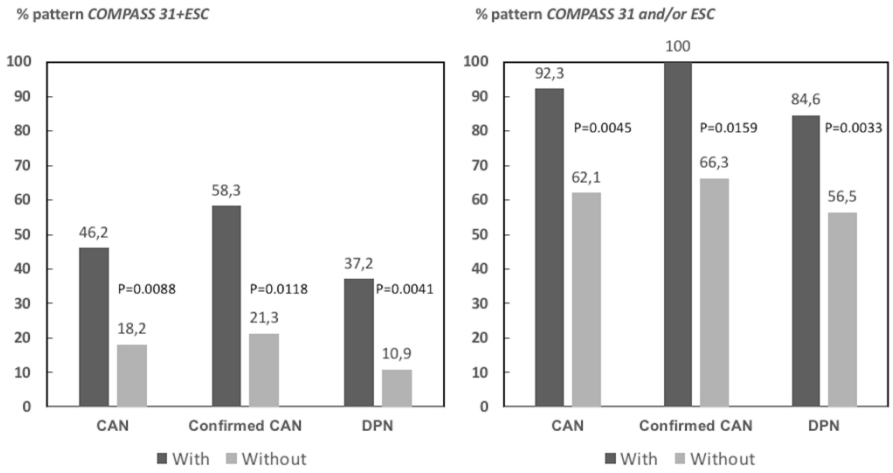

Figure 2. Area under the Receiver Operating Characteristic (ROC) curve (AUC) of COMPASS 31 Total Weighted Score (TWS) for CAN, confirmed CAN and DPN

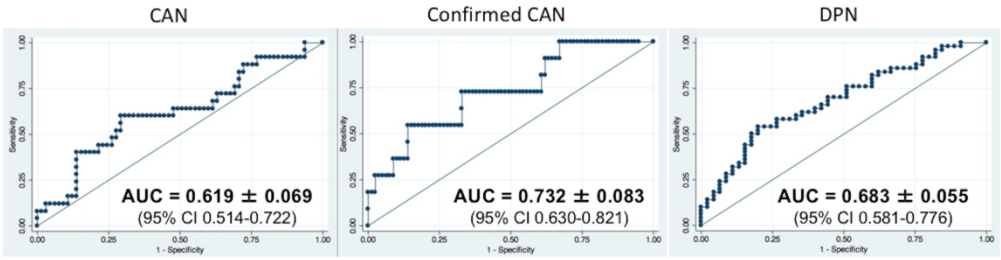

Figure 3. Area under the Receiver Operating Characteristic (ROC) curve (AUC) of ESC feet for CAN, confirmed CAN and DPN