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## Assessment of TB treatment on patient well-being

Dear Editor,

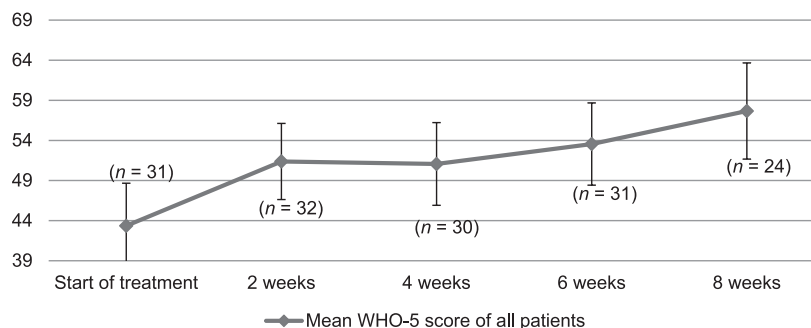
The WHO has set targets to reduce the TB death toll.<sup>1</sup> Support and treatment for all those affected by TB are therefore essential. Treatment outcome depends on the health setting and availability of care, adherence to medication and nutrition, but also, on psychological well-being.<sup>2,3</sup> Studies have assessed the impact of TB on psychological well-being and health-related quality of life (HRQoL). TB patients with a higher score on HRQoL at baseline were more likely to have favourable treatment outcomes.<sup>4</sup> A study conducted in the United Kingdom showed that TB patients had significantly worse HRQoL at diagnosis than UK general population norm scores, suggesting an impact of TB on patient HRQoL.<sup>5</sup> There is a lack of knowledge about the long-term effect of TB and its treatment on well-being. Relatively few studies have assessed well-being or HRQoL in hospitalised TB patients, and none have used the WHO Well-Being Index (WHO-5).<sup>4–6</sup> This short questionnaire, which is available in over 30 languages, consists of five items about vitality, happiness and general interests, and thus measures subjective psychological well-being.<sup>7</sup> It has been used in different fields, including neurology, cardiology and HIV.<sup>8,9</sup> The primary aim of our exploratory study was to investigate subjective psychological well-being using the WHO-5 in TB patients undergoing treatment. A secondary aim was to explore any potential correlation between inflammation and well-being.

Data were retrieved from patients admitted to the TB Center Beatrixoord, Groningen, The Netherlands, between September 2018 and December 2019. As the WHO-5 questionnaire was part of routine care, the Ethics Review Board of the University Medical Center Groningen, Groningen, the Netherlands, waived the requirement for consent (M19.233910). Data were collected from patients aged  $\geq 18$  years, if their first WHO-5 was taken within the first 2 weeks after the start of treatment and if they were admitted for at least 8 weeks. The WHO-5 was filled out every 2 weeks ( $\pm 1$ ). In the first measurement, patients were asked to reflect on the 2 weeks before admission. A medical social worker explained the WHO-5 questionnaire to the patient before asking them to fill it out, and assessed whether the patient had understood the test. If the questionnaire was not clear, the patient filled it out together with the social

worker, often with a certified interpreter joining by phone. After the first time, the questionnaire was filled out by patients themselves. The most recent version of the questionnaire was used,<sup>10</sup> and a translation was used, if necessary. The version in Tigrinya (language of Eritrea) was translated by a professional translation institute (Tolk- en Vertaalcentrum, Hengelo, the Netherlands). It typically took less than 3 minutes for patients to complete the questionnaire. The WHO-5 consists of five statements, which had to be rated from 0 (at no time) to 5 (all the time). The Dutch population norm score is 65.<sup>11</sup> A WHO-5 score of  $< 28$  indicates clinical depression.<sup>12</sup> A score  $< 50$  was used as an indicator of reduced well-being.<sup>12</sup> An improvement of 10 points was considered clinically significant,<sup>12</sup> also called minimal clinically important difference (MCID).<sup>13</sup> We used C-reactive protein (CRP) measured weekly as a surrogate marker for inflammation.

Between September 2018 and December 2019, all 106 potentially eligible patients were assessed. In total, 33 patients (with 16 nationalities) met the inclusion criteria and were included in the analyses; not all patients provided data at all time-points (see Figure). The population studied was predominantly male (87.9%); ages ranged from 19 to 73. Five patients had multidrug-resistant TB (MDR-TB), one patient had extensively drug-resistant TB (XDR-TB). Among the reasons for excluding the other 27 patients were more complex TB and socio-economic reasons (e.g., substance abuse), which was almost 40%. Trends in mean WHO-5 scores for all patients is shown in the Figure. The increase from 43 at baseline to 58 after 8 weeks of treatment exceeded the MCID, and was statistically significant ( $P = 0.002$ ). The scores in our population were significantly lower at every time-point than the Dutch population norm scores, except for the final point at 8 weeks. Norm scores for heterogenous population like ours are lacking. This corresponds to the findings of other studies, which suggest that, although treatment has an obvious positive effect on QoL, patients continue to suffer from diminished QoL after 1 month of treatment.<sup>5,6</sup>

The first score was  $< 50$  in more than half of the patients ( $n = 18$ ). Their mean score improved considerably during treatment (more than all patients combined), but did not reach the same end-level. The long-term outcomes of the patients included in this



**Figure** Trends in mean WHO-5\* scores of all patients (vertical bars = standard errors).<sup>†</sup> \*5-item WHO Well-Being Index. <sup>†</sup>All timepoints have a margin of 1 week.

study was not yet known. At any time-point, 18 patients had a score under 28, which may indicate clinical depression.<sup>12</sup> However, none of them were diagnosed with mood disorders. Drug resistance (MDR-TB or XDR-TB) and substance abuse had no statistically significantly different impact on WHO-5 scores. The mean score on all individual statements increased significantly between time of admission and 8 weeks into treatment. Statement 3 (active and vigorous) showed the worst mean score at admission, but improved significantly, which may indicate good physical rehabilitation of the patients. The mean score on statement 5 (patients' interests) was low and improved slightly, which may indicate that boredom was still a major issue in hospitalised TB patients. Previous TB and HIV studies did not report differences in scores based on the different WHO-5 questions.

The inflammation caused by TB generally decreases during treatment<sup>14</sup> and psychological well-being and HRQoL improve during treatment,<sup>5,6</sup> suggesting an inverse relation between inflammation and psychological well-being. The median CRP declined rapidly during the first 2 weeks of treatment, and declined further until 8 weeks into treatment. However, Pearson correlation showed no significant association ( $P = 0.089$ ) between the decrease in inflammation and the increase in well-being. Although depression has been linked to inflammatory status,<sup>15</sup> no other studies on infectious diseases were found that assessed the relation between well-being or HRQoL and CRP.

Previous studies using extensive questionnaires have suggested that TB may have a substantial impact on patient QoL. This exploratory study shows that the WHO-5 is a valid, easy-to-use means of assessing subjective psychological well-being in TB patients. The improvement in patients' subjective psychological well-being was easy to monitor and improved considerably during treatment. The WHO-5 instrument adds the patients' perspective to classical response markers. Until good biomarkers to predict

outcomes are available, easy-to-use mental and physical response markers during treatment deserve further evaluation.

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