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Abstract

Background: Preterm infants and infants with perinatal brain injury show higher incidence of neurodevelopmental disorders (NDD). The Infant Motor Profile (IMP) is a clinical assessment which evaluates the complexity of early motor behaviour. More data are needed to confirm its predictive ability and concurrent validity with other common and valid assessments such as the Alberta Infant Motor Profile (AIMS) and the Prechtl's General Movement Assessment (GMA). The present study aims to evaluate the concurrent validity of IMP with AIMS, to assess its association with GMA, to evaluate how IMP reflects the severity of the brain injury and to compare the ability of IMP and AIMS to predict abnormal outcome in 5-months infants at risk of NDD.

Methods: 86 infants at risk of NDD were retrospectively recruited among the participants of two clinical trials. Preterm infants with or without perinatal brain injury and term infants with brain injury were assessed at 3 months corrected age (CA) using GMA and at 5 months CA using IMP and AIMS. Neurodevelopmental outcome was established at 18 months.

Results: Results confirm a solid concurrent validity between IMP and AIMS (Spearman's ρ 0.76; p<.001) and significant association between IMP and GMA. Unlike AIMS, IMP Total score accurately reflects the severity of neonatal brain injury (p<.001) and results to be the strongest predictor of NDD (*p*<.001). Confrontation of areas under receiver operating characteristic curves (AUC) confirms that IMP Total score has the highest diagnostic accuracy at 5 months (AUC 0.92). For an optimal IMP cut-off value of 70, the assessment shows high sensitivity (93%) and specificity (81%) (PPV 84%; NPV 90%).

Conclusions: Early motor behaviour assessed with IMP is strongly associated with middle-term neurodevelopmental outcome. The present study confirms the concurrent validity of IMP with AIMS, its association with GMA and its ability to reflect brain lesion load contributing to the construct validity of the assessment.

Background

In the last decades, the increasing survival rates of preterm and high-risk full-term infants is becoming a reason for growing concern about their neurodevelopmental outcome. Consequences may include different forms of neurodevelopmental disorders (NDD). The term NDD includes a wide range of neurological and psychiatric conditions such as cerebral palsy (CP), social communication disorder, attention deficit hyperactivity disorder (ADHD), and other congenital neural anomalies resulting from a precocious disruption of functional brain connectivity.[1] Early detection of NDD is becoming one of the greatest challenges in developmental neurology since it has been proven that response to an intervention is far more effective if provided during early infancy, when brain plasticity is at the highest levels.[2]

It is widely accepted that standardized follow-up programs are crucial for the early detection of NDD; nevertheless, the identification of the right diagnostic instruments to be used at the right time is still matter of debate. Indeed, an ideal clinical instrument should be able to detect early signs of atypical development and to predict the severity of the outcome. So far, an extensive amount of neuromotor assessments has been proposed. Among them, Prechtl's General Movements Assessment (GMA) resulted to be highly reliable in the prediction of long term neurologic dysfunctions during the first months of life.[3],[4] GMA is based on a standardized qualitative analysis of infant's spontaneous motor repertoire in which factors like variability, distribution and complexity of movements reflect the pattern of typical and atypical development. However, after 4 to 5 months post-term age spontaneous general movements gradually fade-out, leaving room for a new complex repertoire of intentional goal-directed movements. At that age GMA cannot be performed and, for such reason, there is need for other standardized assessment tools providing insight not only about the presence of specific neurological signs but also about the quality and variability of motor behaviour.

A growing amount of literature seems to indicate that instruments assessing the *quality* of motor behaviour can provide more subtle information about the brain functioning of small infants rather than a traditional neurological evaluation.[5] In general, the evaluation of quality and especially variability of the early motor repertoire seems to reflect brain functional integrity and connectivity in a much more accurate way. As a result, these kind of qualitative assessments turned out to be useful not only for the prediction of major motor disorders (such as CP) but also for the identification of early signs of other NDD.[4],[6]

In this framework, the Infant Motor Profile (IMP) assessment has been developed.[7] IMP is a video-based assessment of motor behaviour of infants from 3 months of corrected age (CA) until the age of autonomous

walking (approximately 18 months). IMP has been developed on the assumption that qualitative aspects of movement such as variation (size of the motor repertoire) and adaptability (ability to perform a selection of movement strategies out of the whole motor repertoire) are much more informative than the mere achievement of motor milestones.[8] Indeed, the instrument consists of 80 items classified into five domains; three of them are qualitative (Variation, Adaptability and Fluency) and two are related to performance (Performance and Symmetry). The scoresheet provides the IMP Total score and separate results for each domain.

After the first description by Heineman et al (2008), the authors reported a strong correlation between IMP and other widely used assessment tools such as the Alberta Infant Motor Scale (AIMS) and a satisfactory inter-rater reliability.[9] Later on, they explored the association between IMP values and later cognitive and motor impairment. In 2011, they longitudinally assessed a group of preterm and full-term infants using IMP at 4, 6, 10 and 12 months showing a high ability to predict CP at 18 months.[10] Recently, the same group demonstrated a clear relationship between developmental motor trajectories measured with IMP and later outcome at school age.[11] These findings support the idea that variability of early motor repertoire could represent not only an early marker of major motor disorders but also of neurodevelopmental disorders as a whole.

Nevertheless, these studies mainly involved infants being at relatively low risk for NDD (e.g. children of parents with reduced fertility or term infants with no additional risk factors)[8],[10–12] raising the need to explore the relation between IMP and outcome in high risk populations. Moreover, as neonatal brain ultrasound and MRI is becoming increasingly important in the prognosis of at-risk infants, the relation between the imaging findings and IMP still needs to be fully elucidated.

The aims of the present study were: to confirm the concurrent validity of IMP with AIMS in a selected population of infants at risk for NDD, to evaluate its association with GMA, to investigate how IMP reflects the severity of the brain injury and to compare the predictive ability of IMP and AIMS in a population of selected infants with an increased risk of NDD.

Methods

Participants

We retrospectively recruited eighty-six infants among the participants of two clinical trials (ClinicalTrials identifier NCT01990183, NCT03234959). Both trials addressed a population of infants considered to be at risk of NDD having the following inclusion criteria: preterm infants with or without brain injury and term infants with perinatal brain injury. Infants with polymalformative syndromes, cerebral malformations, severe sensory loss (retinopathy of prematurity (grade >II)) were excluded. As per protocol, all infants had a clinical follow-up of 18 months. Both trials have been approved by the Tuscan Region Paediatric Ethics Committee.

Data collection and measurements

All subjects were recruited during the hospitalization in the NICUs or during the follow-up programs for high risk infants of three different referral centres: the Neonatal Intensive Care Unit of the "University Hospital Santa Chiara" in Pisa, the Neonatal Intensive Care Unit of "Meyer Children's Hospital" in Florence and the Neonatal Intensive Care Unit of "Careggi University Hospital" in Florence. Informed consent forms were signed by parents or legal representative of eligible infants.

After discharge from the NICU, all patients were assessed at 3 months, 5 months and 18 months of CA. At 3 months of CA, Prechtl's Assessment of General Movements (GMA) was performed independently from pre-recorded videos by two experienced assessors certificated from the GMs Trust. Physiologic fidgety movements were classified as normal (normal fidgety movements) or not normal (absent fidgety, sporadic fidgety, abnormal fidgety movements).[13] In case of disagreement among the two assessors, the video was discussed until agreement on a final score was reached. At 5 months CA, all infants where assessed with IMP and Alberta Infant Motor Scale (AIMS). All the clinical assessments were video recorded and subsequently scored off-line by a trained assessor (VM). As previously described by Heineman and et al., since infants under the age of 6 months show limited ability to select appropriate strategies from the motor repertoire, the Adaptability domain was not assessed.[7,14] Final outcome was determined at 18 months CA after a clinical neurodevelopmental assessment performed by a child neurologist. Additional clinical assessments (Bayley-III, ADOS-2, MABC-2…) were individually chosen according to the clinical picture. The presence of a NDD was defined according to the DSM5 criteria by the presence of a significative impairment in motor, cognitive or social functions including CP, global developmental delay, social communication disorders, behavioural disorders, fine motor and coordination dysfunctions.[15]

Serial cranial ultrasonography (cUS) were performed in the NICUs. When cranial ultrasound was suggestive of brain injury, infants were further investigated with brain magnetic resonance imaging (MRI). Term and preterm infants with history of showing any sign of neurological disease (hypoxic-ischemic encephalopathy, stroke,

seizures…) were scanned with MRI as part of the standard clinical care. cUS and MRI images were evaluated in order to provide an overall stratification between: a) absence of lesions; b) mild/moderate brain injury (preterm white matter injury grade I-II,[16] intraventricular haemorrhages grade I-III,[17] hypoxic-ischemic injury with predominant watershed pattern,[18] ischemic stroke without basal ganglia involvement, small unilateral haemorrhagic infarction); c) severe injury (preterm white matter injury grade III, hypoxic-ischemic injury with predominant basal ganglia-thalami pattern, extensive bilateral haemorrhagic infarction, ischemic stroke with basal ganglia involvement or asymmetry of the posterior limb of the internal capsule).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25.0 for Mac (IBM Corporation, Armonk, NY). Demographic and clinical summaries (sex, gestational age, brain injury and GMA) were computed for each subgroup. Normality of data distribution was verified by Shapiro-Wilk's Test and in relation to the non-normal distribution of the majority of the data, non-parametric analyses were used. For the concurrent validity analysis, the Spearman's rank correlation coefficient (ρ) was calculated to examine the association of IMP scores with AIMS scores. Correlation was defined as strong for values of $\rho > 0.75$, moderate for values of ρ 0.50-0.75, fair for values of ρ 0.25-<0.50, weak for values of $\rho < 0.25$.[19] Distribution of IMP and AIMS values in relation to the GMA was evaluated with the Mann-Witney test. The association between IMP scores and severity of the brain injury was assessed using the Kruskal-Wallis test followed by a pairwise multiple comparison of mean ranks. For the prediction analysis, correlations between IMP scores, AIMS scores and clinical outcome was tested with the Mann-Witney test; individual U coefficients were reported separately for each domain. A binary logistic regression model was used to estimate the ability of IMP total score and AIMS score to predict the outcome applying the forced entry method. Hosmer-Lemeshow test was used to determine the goodness of the fit. Predictive power of the model was calculated from the Nagelkerke's R2 and the overall accuracy of the classification.

Finally, receiver operating characteristic (ROC) curves were computed to assess the individual predictive ability of IMP and AIMS and to provide possible optimal cut-off points at 5 months CA for the prediction of NDD. Values of areas under the ROC curve (AUC) of 0.50 suggested no diagnostic accuracy of the test, values of 0.50-0.70 were considered to indicate poor discrimination, values of 0.70 - 0.80 were considered acceptable, 0.80 - 0.90 was regarded as excellent; values over 0.90 were considered outstanding.[20] Differences and correlations with p<.05 were considered statistically significant.

Results

Mean gestational age of the study sample was 32 weeks (range 24+5 – 40+5; SD 3.9). Mean age at IMP assessment was 4.9 months (range 4.0-6.0; SD 0.63). 34 infants presented perinatal brain injury (namely haemorrhagic infarctions, stroke or preterm white matter injury). Clinical characteristics of the study sample is presented in Table 1. At 3 months 33 infants (38.4%) showed sporadic or absent fidgety movements at the GMA; no abnormal fidgety movements were reported. A high interscorer agreement was reached among the assessors on the first evaluation of GMs (Cohen's kappa=0.80); following discussion, agreement was reached for the totality of the assessments. All infants included in the study completed the follow-up at 18 months CA. At the end of the study 27 patients (31.4%) presented a NDD, 59 (68.6%) were considered as typical. Among the 27 infants with NDD, the prevalent diagnosis was CP in 14, followed by minor motor disorders in 6, cognitive impairments in 5, social communication disorders in 2.

Table 1. Demographic and clinical characteristics of the study sample.

	Typical, n (%) n=59	NDD, n (%) n= 27
Sex		
Male (n=46)	34 (73.9%)	12 (26.1%)
Female (n=40)	25 (62.5%)	15 (37.5%)
Gestational Age		
25-31 weeks (n=44)	33 (75.0%)	11 (25.0%)
32-36 weeks (n=27)	21 (77.8%)	6 (22.2%)
37-41 weeks (n=15)	5 (10.0%)	10 (90%)
Brain injury		
No brain injury (n=52)	49 (94.2%)	3 (5.8%)
Mild/moderate injury (n=14)	8 (57.1%)	6 (42.9%)
Severe brain injury (n=20)	2 (10.0%)	18 (90.0%)
GMA		
Normal Fidgety (n=53)	49 (92.5%)	4 (7.5%)
Not Normal (Absent / Sporadic) Fidgety (n=33)	10 (30.3%)	23 (69.7%)

Concurrent validity of IMP with AIMS

A clear and statistically significant relation between IMP values and AIMS total values was evident for the IMP total score and almost all of the domain scores. IMP Total and Performance showed a strong correlation with AIMS (Spearman's ρ 0.76 and 0.89 respectively; $p<.001$). Correlation of IMP Variation and Symmetry with AIMS were moderate (Spearman's ρ .58 and .56 respectively; $p<.001$).

IMP and GMA Assessment

The distribution of IMP Total scores resulted significantly different between infants with normal and not normal fidgety movements at the GMA (Mann-Whitney U = 83; $p<.001$) suggesting a strong association between the two assessments (Figure 1). Distribution of AIMS values resulted in a weaker association (Mann-Whitney U = 235; $p<.001$).

Correlation of IMP and AIMS to neuroimaging data

Both IMP Total ($p<.001$) and AIMS ($p<.05$) scores correlated with the presence and severity of the brain injury at the neonatal brain MRI (Table 2). All of the IMP domain scores showed individual correlation with the severity of the lesion load (Variation, Symmetry, Performance $p=<.001$; Fluency $p<.05$). Post-hoc analysis for each group showed significant correlation only for the IMP Total score ($p<.001$).

Table 2. Distribution of scores among MRI severity classes

	No brain lesions mean (SD)	Mild/Moderate injury mean (SD)	Severe injury mean (SD)	*p* value	
IMP Total Score	74.5 (3.2)	71.0 (4.1)	63.5 (5.0)	<.001	*
IMP Variation	70.1 (6.7)	69.2 (5.2)	61.3 (4.8)	<.001	
IMP Fluency	75.3 (1.6)	73.2 (7.4)	72.9 (6.0)	.007	
IMP Symmetry	97.2 (4.3)	92.0 (4.4)	74.6 (14.4)	<.001	
IMP Performance	55.0 (6.0)	51.3 (6.7)	46.8 (7.3)	<.001	
AIMS Total Score	14.7 (3.5)	13.4 (2.8)	10.4 (2.8)	<.05	

Predictive validity of IMP and AIMS

Distribution of IMP and AIMS scores in respect of the outcome at 18 months are reported in Table 3.

Table 3. Distribution of scores at 5 months in infants with typical development and neurodevelopmental disorders (NDD). *p* values and *U* coefficients of the Mann-Whitney *U* test.

	Typical	NDD		
	Mean	Mean	*p* value	*U* coefficient
	(SD)	(SD)		
IMP Total Score	74.3 (3.1)	64.9 (5.4)	<0.001	83
IMP Variation	70.5 (6.4)	62.4 (5.1)	<0.001	254
IMP Fluency	75.3 (2.2)	72.5 (6.9)	0.01	646
IMP Symmetry	96.6 (4.6)	79.0 (14.5)	<0.001	131
IMP Performance	55.0 (5.8)	47.0 (7.1)	<0.001	309
AIMS Total Score	14.8 (3.4)	10.6 (2.6)	<0.001	234

IMP Total score at 5 months showed a highly significant relation with the neurodevelopmental outcome: infants with a typical development showed substantially higher score (mean 74.3; SD 3.1) than infants with NDD (mean 64.9; SD 5.4); *p*<.001 (see Fig.1). Variation, Symmetry and Performance confirmed to be individually correlated with the neurodevelopmental outcome (*p*<.001). Also, AIMS was correlated to the neurodevelopmental outcome (*p*<.001). In logistic regression, IMP Total score confirmed to be the best single predictor of NDD (*p*<.001): the model based on the IMP Total confirmed a good fit (Hosmer-Lemeshow's P=.67) and a good predictive power (Nagelkerke's R2 = 0.737) with an overall accuracy of classification of 88%. Fig. 3 shows a graphical representation of the probability to develop a NDD according to the model based on IMP Total score values. A similar model based on AIMS score showed a lower predictive power (Nagelkerke's R2 = 0.445).

ROC curves generated from the IMP Total score and the AIMS Total score are reported on Fig. 4 summarizing the overall diagnostic accuracy of the two assessments. The Area Under the Curve (AUC) for the IMP Total score

resulted outstanding (0.95; p<.001; CI95% 0.90-0.99) while the AUC for the AIMS score was lower (0.85; p<.001; CI95% 0.77-0.94) indicating that IMP presents higher accuracy in the early detection of NDD. The definition of an optimal cut-off point of 70 allowed to obtain an overall sensitivity of 93% and a specificity of 81% in the prediction of NDD (PPV 84%; NPV 90%).

Individual ROC curves were developed for each IMP domain: AUC values for the IMP Variation, Symmetry and Performance showed excellent accuracy whereas values for IMP Fluency indicated poor prediction (see Table 4).

Table 4. Area under the ROC curves for IMP Total score and domains score.

	Area under the ROC curve (95% CI)	*p* value
IMP Total Score	0.95 (0.90-0.99)	<.001
IMP Variation	0.84 (0.75-0.93)	**<.**001
IMP Fluency	0.59 (0.45-0.72)	.194
IMP Symmetry	0.92 (0.85-0.98)	<.001
IMP Performance	0.81 (0.69-0.92)	<.001
AIMS Total Score	0.85 (0.77-0.94)	<.001

Discussion

Our data confirm an excellent concurrent validity of IMP and AIMS. Values are in line with data previously published by Heineman et al.[7] confirming a maximal correlation for the IMP Performance and lower correlation for the IMP Fluency. The highest correlation between IMP Performance and AIMS is explainable as both are focused on gross-motor achievements. Not surprisingly, association between IMP and GMA was also good indicating that both assessments reflect the same qualitative elements as variation, symmetry and fluency of movements.

In the definition of prognosis of children at risk of NDD, correlation between clinical and neuroradiological tools is pivotal. In our study, IMP Total score reflected the presence and the severity of brain injury more accurately

then AIMS. These data supports the idea that any neurological condition which affects the complexity of brain connectivity results in a reduction of the complexity of motor repertoire.[21] This subtle and complex process is better captured by qualitative assessments such as IMP rather than performance-based tools such as AIMS.

We compared the ability of IMP and AIMS to predict the neurodevelopmental outcome in a population of infants specifically selected for being at risk of NDD. While both tests confirmed to be significantly correlated to NDD, IMP Total score resulted to be the most accurate single predictor of atypical outcome. At 5 months CA, after the identification of a cut-off value of 70, IMP Total score predicted NDD with high sensitivity (93%) and specificity (81%). Among the different subscores, all domains except for Fluency resulted significantly related to the outcome. IMP Fluency reflects the ability of infants to perform refined movements in different conditions (e.g. sit, supine, walking...). The domain is composed by only 7 items (6 for non-walking infants) mostly investigating to the presence of tremors and non-fluent movements during the assessment. Unlike previously published data,[11,22] the majority of our study sample scored the same low value on this domain (75 points); also, IMP fluency at 5 months was poorly corelated to the presence of brain injury and showed no significant relation with the neurodevelopmental outcome. A possible reason for this might be related to the different characteristics of our study population which was largely selected among infants who experienced prolonged hospitalizations in NICU. Indeed, if on the one hand lack of fluent movements could be one of the first indicators of non-optimal neurologic development, it is also true that benign shudders, jitteriness and tremors are commonly seen during the first months of life, especially in infants with prolonged staying in NICU.[23,24] Also, the small number of items contributing to the IMP Fluency score resulted in a reduced variability of the values.

This is the first work, provided by a group who is independent from the developers of the scale, evaluating the predictive validity of IMP in a population of at-risk infants. A strength of the study is the presence of three different video-based assessments which were scored by blind assessors. Another strength is the fact that all the infants were recruited at the very early stages of life among infants being at risk of NDD. Nevertheless, the study presents several limitations. First of all, the short duration of follow-up and the absence of a wide-range battery of assessments at 18 months could have prevented from the identification of milder conditions which require more time and standardized assessments for the diagnosis. Infants were retrospectively recruited among the participants of two clinical trials during which an 8-weeks intervention program based on infant massage or telerehabilitation was provided; a mild effect of these programs on the final outcome cannot be ruled out.[25,26] Furthermore, we provided a coarse classification of brain imaging since no widely used classification system of perinatal brain

injury takes into account both term and preterm patterns of injury. Our classification might not accurately reflect the actual severity of some pattern of brain injury.

Conclusion

Accurate prediction of NDD during the first months of life is paramount in order to provide children at risk an early access to rehabilitative intervention. Literature supports the combined use of GMA and brain MRI for an early prediction of NDD. However, when GMA is not available after 5 months, a qualitative assessment of motor behaviour with IMP represents a valid and reliable alternative. The high flexibility, the absence of need for expensive kit materials and its excellent psychometric performances make IMP an extremely interesting tool in the evaluation of infants at risk for NDD. In this sense, a greater integration of IMP among the clinical tools used during the follow-up programs will be useful. Also, the use of IMP as an outcome measure in clinical trials will provide data on the possible use of this instrument to reflect the effect size of a treatment.

The present study shows that IMP has a high concurrent correlation with two of the most used clinical assessment tools in early infancy (AIMS and GMA). Furthermore, we demonstrated that IMP accurately reflects the degree of early brain injury and that there is a clear relationship between early motor development assessed with IMP and neurodevelopmental outcome. These findings support the idea that at the early stages of development, qualitative aspects of motor behaviour may reflect the complexity of cerebral connectivity thus representing a strong indicator of a future diagnosis of NDD.

Additional observational trials with prospective cohorts of at-risk infants should further elucidate the relationship between early motor behaviour and neurodevelopment, especially investigating how different patterns of brain injury affect the different IMP domains.

List of abbreviations: Attention Deficit Hyperactivity Disorder (ADHD); AUC: Area Under the Curve; GMA: General Movement Assessment; IMP: Infant Motor Profile; MRI: Magnetic Resonance Imaging; CP: Cerebral Palsy; NICU: Neonatal Intensive Care Unit; NDD: Neurodevelopmental Disorder

Declarations

Ethics approval and consent to participate

This trial has been approved by the Tuscan Region Paediatric Ethics Committee. Informed consents were signed by parents or legal representative of eligible infants.

Consent for publication

Informed consents for data publication were signed by parents or legal representative of eligible infants.

Availability of data and materials

The dataset analysed during the current study are available from the corresponding author to researchers on reasonable request.

Competing interests

The authors report no competing interests.

Authors' contributions

RR gave a substantial contribution to clinical assessment of infants, the analysis of data and the drafting of the paper. VM and EB administered and scored all the clinical assessments. MLC, AC, MG selected and recruited newborns at high risk being also in charge of the traditional clinical follow-up. GC and GS are responsible for the study design and the approval of the submitted version of the paper. All the authors had complete access to the study data of this work.

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Figure 1

Correlation of Prechtl's General Movement Assessment at 3 months with Infant Motor Profile Total and Alberta Infant Motor Scale at 5 months corrected age. * p<.001

Figure 2

Infant Motor Profile (IMP) scores, Alberta Infant Motor Scale (AIMS) scores at the corrected age of 5 months in children with typical development and neurodevelopmental disorders (NDD). Mann-Whitney U test: *p<.001

Figure 3

Scatterplot of predicted probability of neurodevelopmental disorders (NDD) from the regression model derived from Infant Motor Profile (IMP). Total scores at the corrected age of 5 months. Values ≤ 70 determine a major increase of the probability to develop NDD. Empty markers represent actual typical development, full markers represent actual NDD.

Figure 4

Receiver operating characteristic (ROC) curve of Infant Motor Profile (IMP) Total score and Alberta Infant Motor Scale (AIMS) score as predictors of neurodevelopmental disorders (NDD) at the corrected age of 5 months.
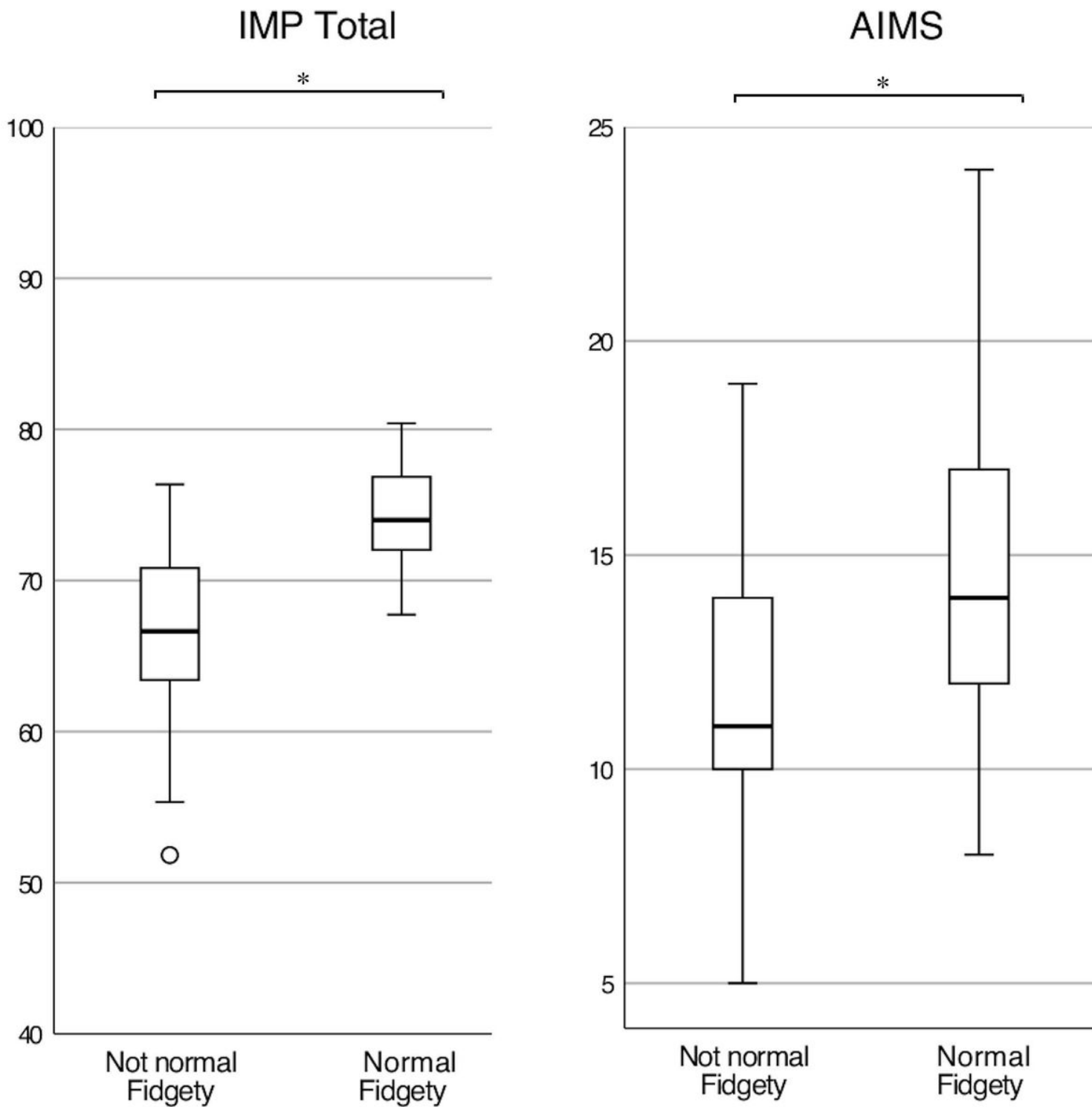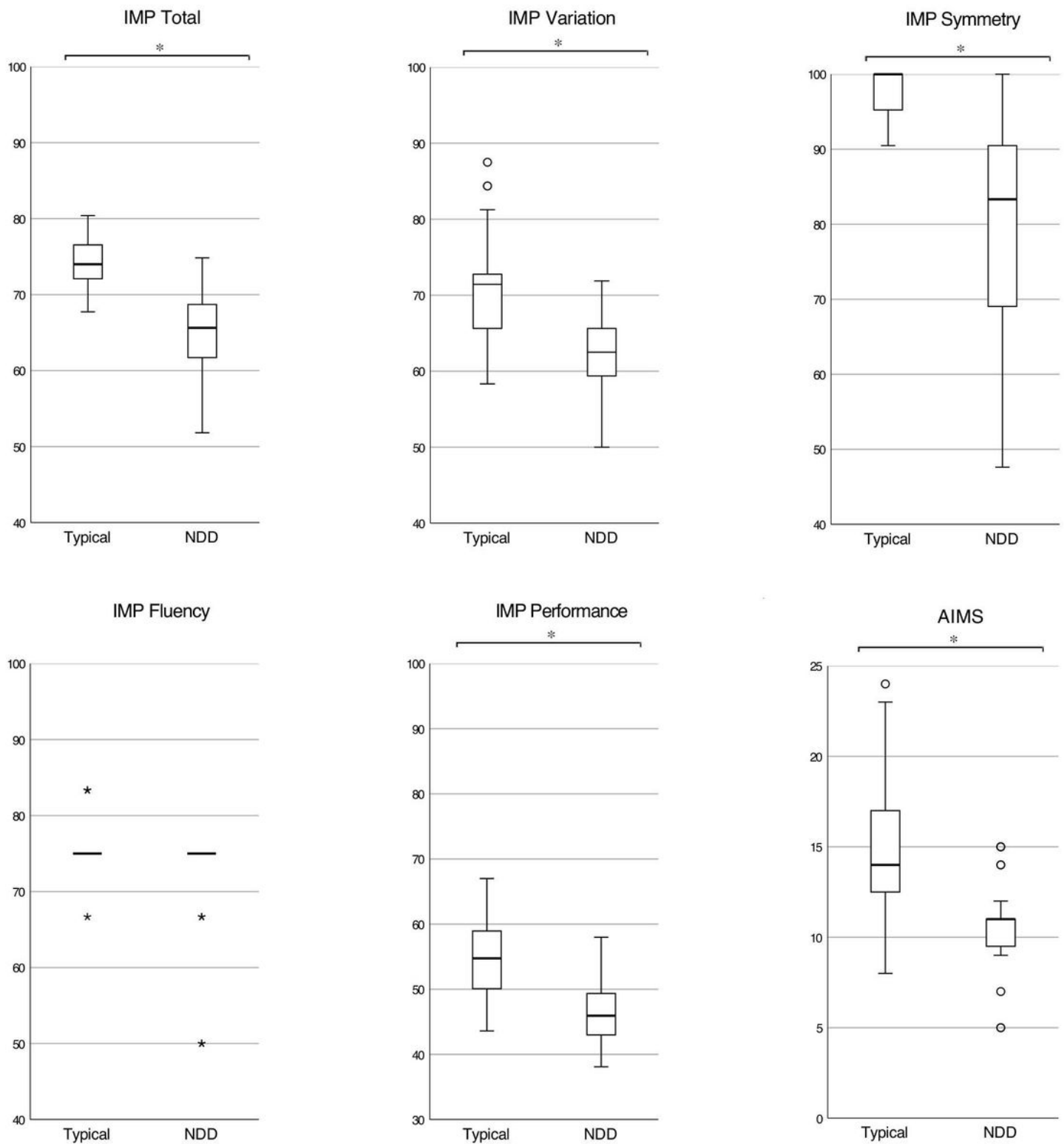
Figures

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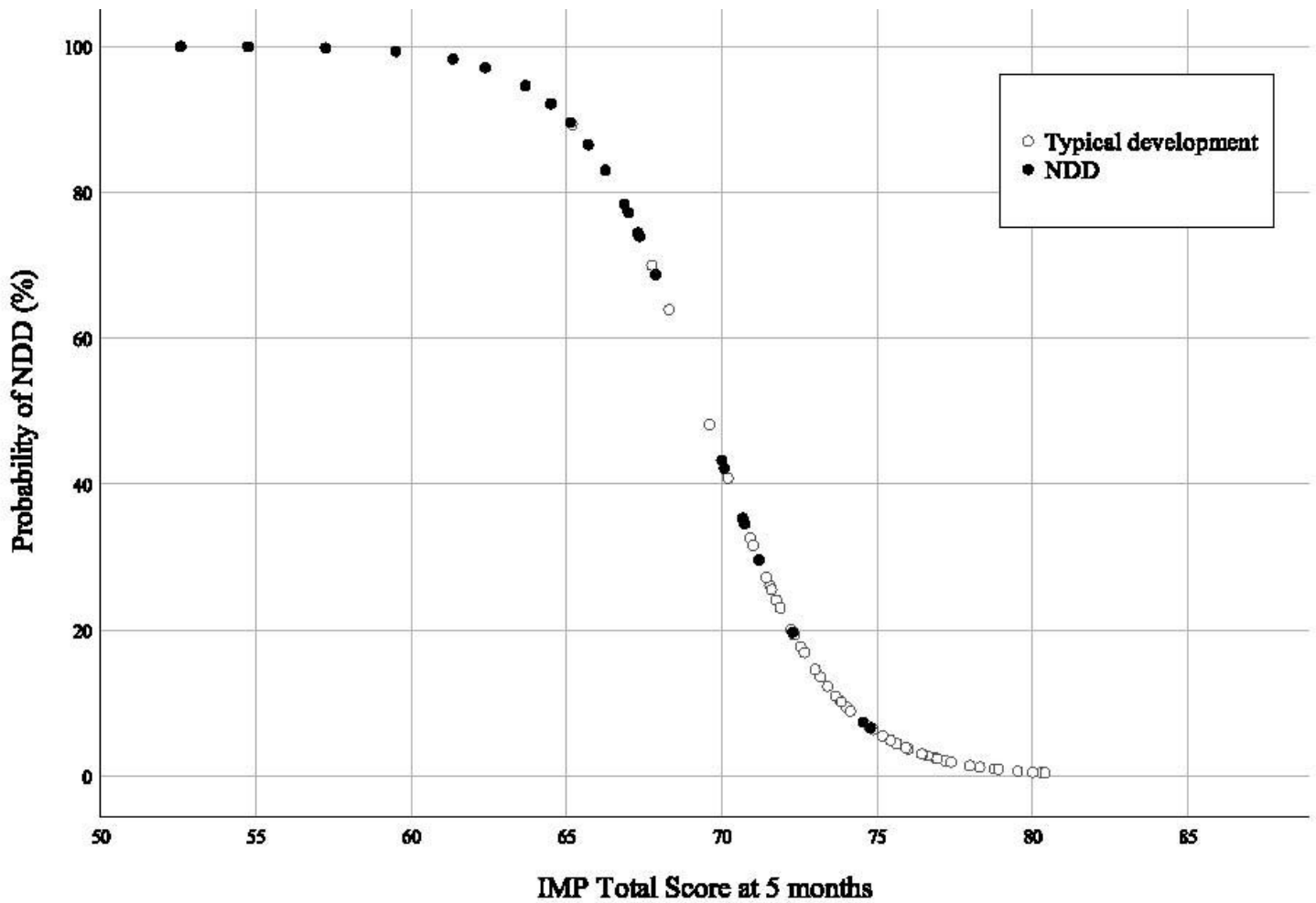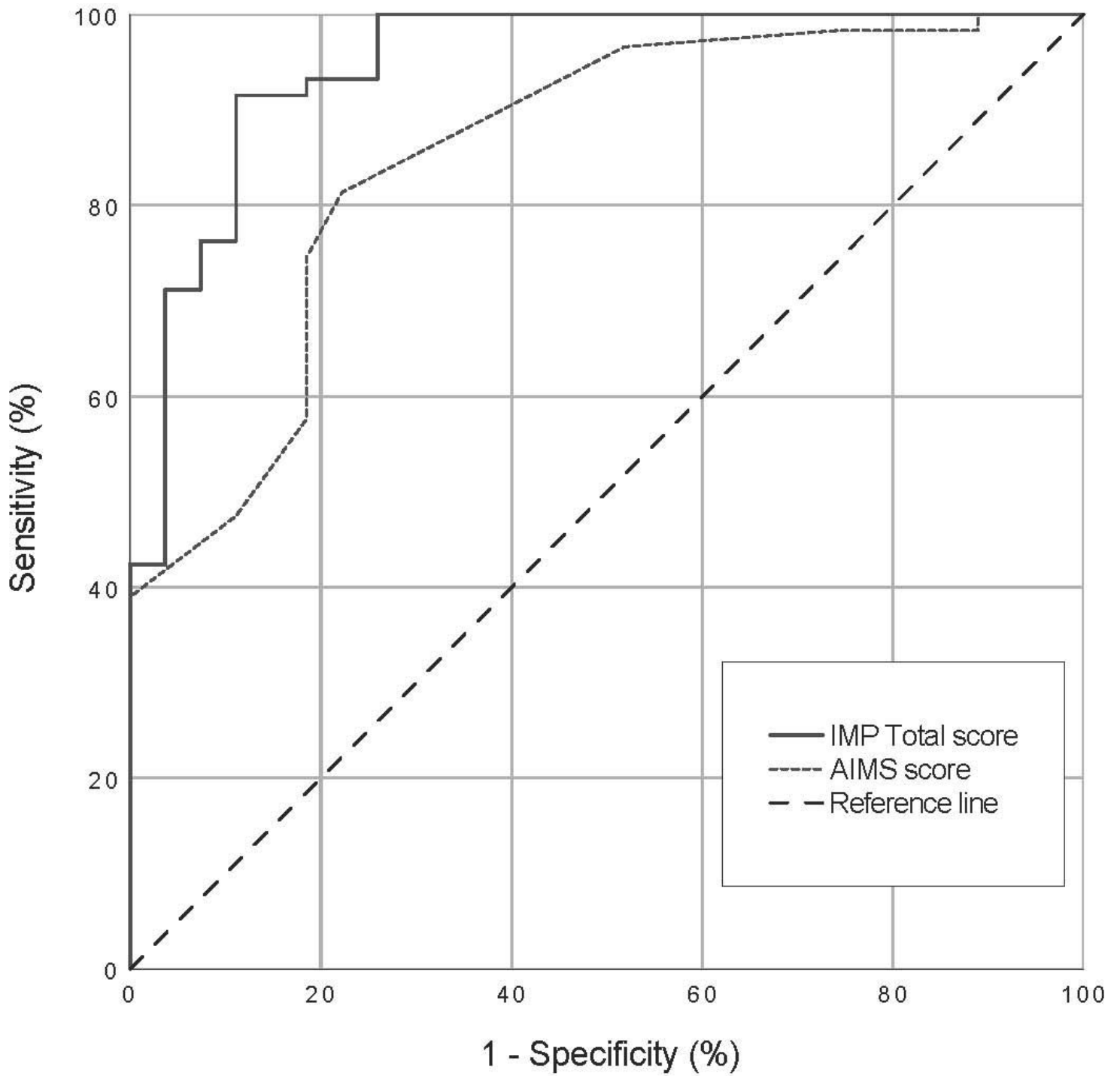
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