Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Effectiveness of Adrenal Venous Sampling in the Management of Primary Aldosteronism: Single-Centered Cross-Sectional Study at a Tertiary Care Hospital in Sri Lanka

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Abstract

Introduction. Adrenal venous sampling (AVS) is the gold standard procedure to discriminate unilateral primary aldosteronism (UPA) from bilateral disease (BPA). AVS is technically demanding and is only performed in a limited number of centers in Sri Lanka. This study aimed to evaluate the effectiveness of AVS in the management of primary aldosteronism.

Methodology. Thirty-two patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were enrolled. Continuous and categorical variables were summarized with mean ± SD and proportions, respectively. Mean and standard deviation of contralateral suppression index (CSI) were estimated with an intercept-only Bayesian inference model.

Results. The adrenal veins were successfully cannulated in 12 (37.5%). Lateralization was established in 11 (91.7%), and one was diagnosed as having bilateral disease. There were no total failures. Right AV cannulation was unsuccessful in 18 (56.25%), out of which lateralization was demonstrated in 9 (50%), while the rest were considered inconclusive. Left AV cannulation was unsuccessful only in 2 (6.25%); one was lateralized, while the other remained inconclusive. Among patients classified as having unilateral disease, the estimated mean of the CSI was 0.33 (89% credible interval: 0.11–0.86).

Conclusion. Despite failure due to procedural difficulties, AVS remained useful in the management of patients with PA. CSI remains a useful tool when cannulation is unsuccessful, especially on the right side.

Key words: adrenal venous sampling, lateralization, contralateral suppression index

INTRODUCTION

Primary aldosteronism (PA) is highly prevalent among patients with drug-resistant hypertension[1] and may be diagnosed in >11% of the patients referred to specialized hypertension centres.[2] Though it is common, it is still underdiagnosed.[3]

There is strong evidence indicating that PA increases the risk of organ damage, including cardiorenal complications, if left untreated. Hence, early diagnosis of affected patients and prompt initiation of specific treatment are crucial for preventing cardiovascular events and reversing damage.[4]

It is essential to differentiate unilateral PA [aldosterone-producing adenoma (APA)] from bilateral PA (idiopathic hyperaldosteronism [IHA]) as the former warrants adrenalectomy, whereas the latter needs lifelong treatment with mineralocorticoid receptor (MR) blockers.[5]

Historically, adrenal computed tomography played a crucial role in diagnosing the culprit lesion in PA.[5] With the increasing identification of non-functional adrenal tumours leading to unnecessary interventions, adrenal vein sampling (AVS) became the gold standard investigation to localize and lateralise the lesion. The only exceptions are in younger patients below 35 years of age with florid disease and the presence of a clear one-sided adrenal adenoma with a normal contralateral gland.[5] Current clinical practice guidelines advocate the use of AVS with measurement of plasma cortisol concentration (PCC) and plasma aldosterone concentration (PAC).[5] Though AVS is a straightforward diagnostic test, globally it is used only in a few centres due to the technical challenges, especially in a developing country like Sri Lanka.

eISSN 2308-118x (Online)
Printed in the Philippines

Received: May 1, 2025. Accepted: June 21, 2025.
Published online first: November 6, 2025.
https://doi.org/10.15605/jafes.040.02.23

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However, apart from very few studies conducted in India, research studies on this area are scarce. So far, no studies have been done on AVS and its impact on PA management in Sri Lanka. Hence, we aimed to evaluate the effectiveness of AVS in the management of primary aldosteronism at a tertiary care hospital in Sri Lanka.

METHODOLOGY

Study design

We conducted a retrospective cross-sectional study from April 2021 to April 2023 at the National Hospital of Sri Lanka (NHSL), a tertiary referral centre for AVS in Sri Lanka.

Data collection and its analysis were approved by the ethics review committee at NHSL.

Study population

A total of 32 patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were enrolled in the study. The diagnostic work-up for primary aldosteronism was done according to the established guidelines.[5,6]

Demographic, clinical, and laboratory data were obtained retrospectively from the electronic records in the Department of Chemical Pathology, NHSL. Study variables collected include (1) patient demographics (age and gender), (2) clinical characteristics (blood pressure, potassium level, aldosterone and renin concentrations, post-saline loading aldosterone concentration), (3) radiological imaging findings, and (4) adrenal venous sampling data.

Radiological imaging

Images from the most recent CT or MRI reports reported by the consultant radiologist prior to AVS were evaluated. Imaging reports were categorized in one of four ways: left-sided lesion, right-sided lesion, bilateral lesions, or no lesion. If a lesion was observed on one adrenal gland and the contralateral gland appeared completely normal, the finding was classified as unilateral, either as left-sided or right-sided, depending on the side of the lesion

Adrenal venous sampling

Adrenal vein sampling (AVS) was performed in either a sequential non-stimulated or, in one case, a stimulated manner, depending on the availability of cosyntropin (synthetic ACTH). Due to the economic crisis in Sri Lanka, cosyntropin was not routinely accessible through the public healthcare system, and patients were required to self-fund it if stimulation was deemed necessary. As a result, non-stimulated AVS was the standard approach, with only one patient undergoing stimulated AVS after independently securing cosyntropin.

The procedure was carried out in a dedicated interventional radiology suite by a consultant interventional radiologist, with real-time support from the endocrinology and chemical pathology teams. After local anesthesia, vascular access was obtained through the common femoral vein using a 5F or 6F sheath under aseptic technique. A hydrophilic guidewire and a diagnostic catheter (typically a Simmons or Cobra catheter for the right adrenal vein and a renal double curve or multipurpose catheter for the left) were advanced under fluoroscopic guidance to selectively cannulate each adrenal vein. AVS was performed in a sequential manner — first the right adrenal vein, followed by the left — with blood samples collected from each adrenal vein and a peripheral vein (usually the inferior vena cava at the level of the renal veins or right atrium) for cortisol and aldosterone measurement.

Samples were immediately handed over to the chemical pathology team present on site to ensure rapid processing and minimize pre-analytical variability.

A cortisol gradient across each adrenal vein and IVC of >5 in a stimulated AVS and that of ≥2 in a non-stimulated AVS was used to establish successful cannulation. The procedure was considered successful when both the right and left adrenal veins were successfully cannulated.

Lateralization index (LI) was defined as the ratio of the high to low cortisol–corrected aldosterone ratio. LI of ≥4 in stimulated AVS and that of ≥2 in a non-stimulated AVS indicated unilateral aldosterone excess, while the values between 3 and 4 were assumed borderline in stimulated AVS.

Contralateral suppression index (CSI) is calculated as the ratio of aldosterone/cortisol in the nondominant side to the periphery (IVC). CSI of <0.5 is highly predictive of contralateral disease.[7]

Serum aldosterone was measured with a competitive two-step chemiluminescent microparticle immunoassay in a Diasorin-Liason fully automated analyser at the Medical Research Institute, Sri Lanka.

Serum cortisol was measured by a competitive two-step chemiluminescent microparticle immunoassay in the ADVIA Centaur XP fully automated analyser at NHSL.

All the samples were transported to relevant laboratories at room temperature and analysed on the day of the collection.

Statistical analysis

The distribution of continuous variables was visualized with kernel density plots and histograms. These variables were summarized using the mean and standard deviation (SD) when they demonstrated a near-normal distribution, and the median and interquartile range (IQR) when they did not. Categorical variables were summarized with frequency tables and presented as percentages.

The inter-observer agreement between AVS and CT was assessed with Cohen's kappa statistic and percentage agreement.

Due to the limited sample size and the nature of the data, a Bayesian statistical approach was adopted to estimate the distribution parameters of the CSI. Given that CSI is a non-negative continuous ratio, a lognormal likelihood function was chosen, as it is a maximum entropy distribution appropriate for modelling positive values. An intercept-only Bayesian inference model was implemented using Markov Chain Monte Carlo (MCMC) sampling. Weakly informative priors were applied for the mean (μ) and standard deviation (σ) of the log-transformed CSI values. This choice was made to provide sufficient regularization while allowing the data to primarily inform the posterior estimates, especially in the context of a small sample size and lack of strong prior knowledge. All patients included in this analysis (n = 12) had successful bilateral AVS.

$CSI \sim \text{lognormal}(\mu,\sigma)$ [Likelihood function]
$\log(\mu)=a$ [intercept-only model]
$a \sim N(0,1)$ and $\sigma \sim \text{uniform}(0,10)$ [prior distributions]

Four MCMC chains were used with 50% warm-up samples. Chain mixing patterns were visualized with trace plots.

Analysis was conducted using R language 4.1.2 and Stan Modelling Language through *rstan* and *rethinking* interface packages.

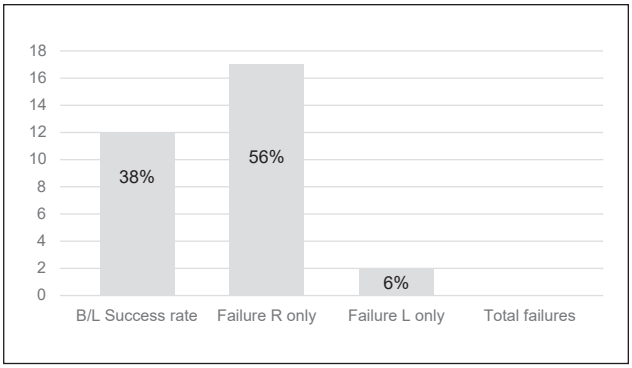

Figure 1. Success and failure rates of AVS.

RESULTS

A total of 32 patients who underwent AVS at the National Hospital of Sri Lanka from April 2021 to April 2023 were included. The mean age of the study population was 52.47 ± 26.14 years, with 19 (59.4%) of them being men. All had hypertension, and 28 (87.5%) had at least one episode of spontaneous hypokalemia.

Of the 32 patients who underwent CT adrenal imaging, 10 had left-sided adenomas, 7 had right-sided adenomas, and 15 had normal adrenal imaging findings.

Success and failure rates

Out of 32 patients, only one underwent stimulated AVS.

There were no total failures in adrenal vein cannulation. Successful cannulation of both adrenal veins was demonstrated (Figure 1) in 12 (37.5%), including the patient who underwent stimulated AVS. Cannulation was unsuccessful on the right in 18 patients (56.25%), compared to 2 patients (6.25%) on the left.

Among those with successful bilateral cannulation, 92% (n = 11) demonstrated lateralization, proving they had unilateral disease, while one patient had bilateral disease. In the group with failed right adrenal vein cannulation (n =18), 50% (n = 9) showed lateralization according to the CSI. Of the two patients with unsuccessful left adrenal vein cannulation, one showed lateralization, and the other had inconclusive results based on the CSI (Figure 2).

No significant procedure-related complications were noted.

Seven patients underwent unilateral adrenalectomy. Histological analysis revealed left-sided adrenal adenomas in five patients and right-sided adrenal adenomas in two. All demonstrated significant improvement in aldosterone and renin values as well as in blood pressure during follow-up. Two patients are awaiting surgery, while the remaining patients are being managed medically.

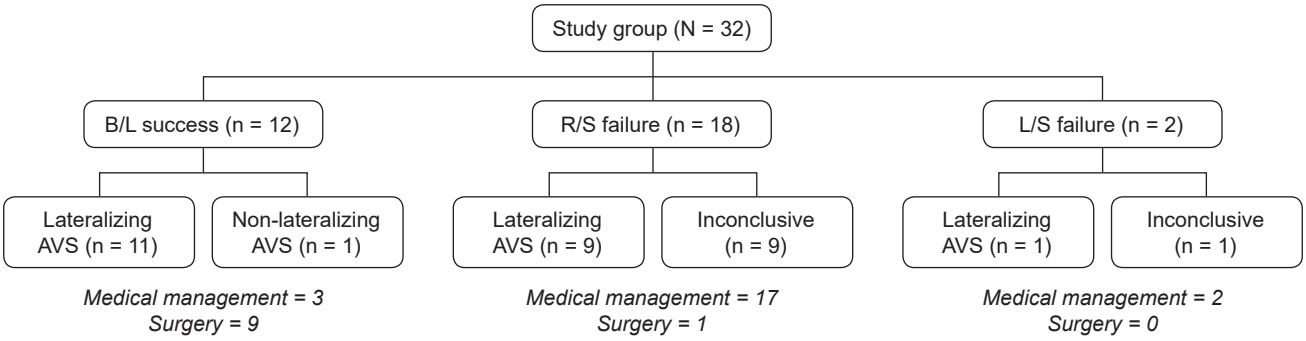

Figure 2. Study profile.

Agreement between AVS and CT findings

CT and AVS results were compared in 12 patients with bilaterally successful AVS, excluding cases with failure in cannulation of either side. The agreement between the two diagnostic methods was 42%. Cohen's kappa statistic was 0.168, indicating a slight agreement. This is depicted in Figure 3.

Estimation of the contralateral suppression index

The Bayesian model demonstrated good convergence, with all four Markov chains showing adequate mixing, as evidenced by trace plot evaluations (Supplementary Figure 1). Among patients classified as having unilateral disease based on adrenal vein sampling, the posterior mean of the CSI was estimated at 0.33, with an 89% credible interval ranging from 0.11 to 0.86 (Figure 4). This distribution supports the utility of CSI in distinguishing unilateral from bilateral aldosterone secretion patterns and aligns with previously suggested thresholds in the literature, though further validation in larger cohorts is warranted.

DISCUSSION

The present study provides a critical understanding of the implementation of AVS in the management of PA at the NHSL. The overall success rate for AVS during this period was 38%, which is on par with the German Conn's registry, which reported successful bilateral adrenal vein cannulation in only 30.5% of patients. Furthermore, success rates in centres performing a small number of AVS are reported to be as low as 8%–10%. However, the successful cannulation rate of both adrenal veins was as high as 95.6% in high-volume centers.[8]

The main challenge in successful AVS is the failure to cannulate the right adrenal vein, which results from either the inability to identify the vessel or the misidentification of the vessel.

In this study, the failure rates of the right and left adrenal veins were 56% and 6%, respectively, This finding is consistent with previous studies, which have shown that the right adrenal vein cannulation failure rate is typically higher, ranging from 30% to 60%.[9,10]

In our study, the endocrinology team opted for surgery in only one patient who lateralized on CSI but had successful cannulation on only one side. For cases involving unsuccessful unilateral cannulation and discordant findings between imaging and CSI results, the team deferred surgery and recommended repeating AVS at a later time.

We found a strikingly high rate (58%) of disagreement between CT/MRI results and AVS results, assuming AVS is 100% accurate in detecting the lateralization of aldosterone secretion. Among patients with successful bilateral cannulation (n = 12), a unilateral abnormality was reported

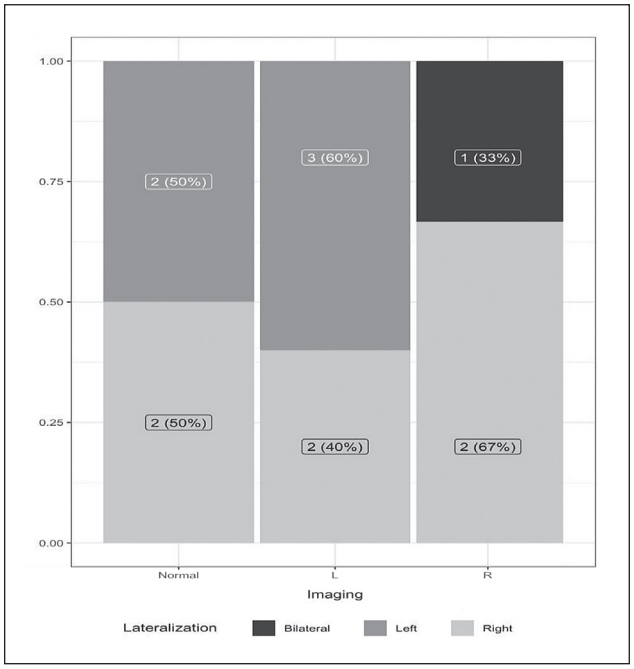

Figure 3. Agreement between adrenal vein sampling (AVS) and CT findings depicted with a width-stacked column chart.

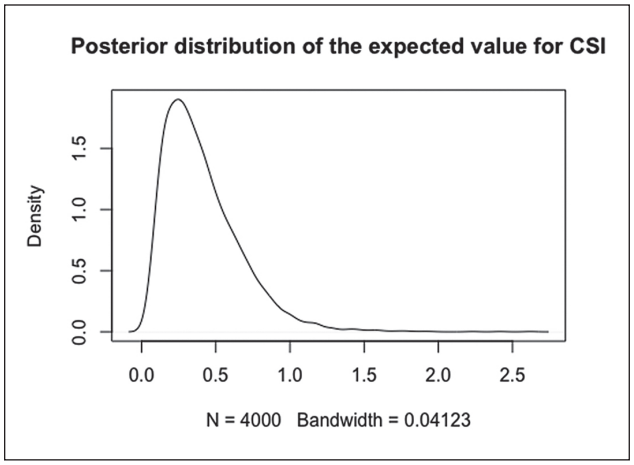

Figure 4. Posterior distribution of the expected value for CSI.

by CT/MRI in 66.6% (n = 8) and by AVS in 91.7% (n = 11). Agreement between CT/MRI and AVS on the involved side was found in only 42% of patients, indicated by a Cohen's kappa statistic of 0.168 (slight agreement). This finding aligns with previous studies that reported a discrepancy between CT/MRI and AVS ranging from 35% to 52%.[8,11]

CT/MRI may detect non-functioning adenomas or nodules, or may fail to detect small functional adenomas, leading to false positive or false negative results. Conceptually, AVS is an attractive procedure because it detects the origin of the abnormality on a biochemical basis in a primarily biochemical disease.

The estimated mean of the posterior CSI distribution was 0.33, which is consistent with the findings by Pasternak

Table 1. Baseline patient data including Contralateral Suppression Index (CSI)

ID	Age	Gender	HT	Hypokalemia	Aldo	Renin	ARR	AVS (S/NS)	Right Cannulation	Left Cannulation	CSI	Lateralized (from AVS)	Imaging
1	71	F	Y	Y			>30	NS	N	Y			L/S lesion
2	34	F	Y	Y	45	0.38	118	NS	Y	Y	0.225	R/S	R/S lesion
3	49	M	Y	Y	30.3	0.12	252	NS	N	Y			L/S lesion
4	60	M	Y	Y	14	0.2	71	NS	Y	Y	2.3	B/L	R/S lesion
5	66	M	Y	Y	20.1	?1.3		NS	Y	Y	0.2	L/S	L/S lesion
6	46	M	Y	Y	18.6	0.11	169	NS	N	Y			Normal
7	48	F	Y	Y			>30	NS	Y	Y	0.48		normal
8	64	M	Y	N	14.3	0.07	204	S	Y	Y	1.5	R/S	L/S
9	46	M	Y	Y	12.9	0.48	26.9	NS	N	Y			normal
10	63	M	Y	Y	10.2	<0.5		NS	N	Y			normal
11	44	F	Y	Y	32	0.5	>30	NS	Y	Y	0.5	L/S	L/S
12	65	F	Y	Y	22.3	0.5	44.6	NS	Y	Y	0.83	L/S	L/S
13	27	F	Y	Y	31.8	0.12	265	NS	N	Y			normal
14	78	F	Y	N	24.3	1	24.3	NS	Y	N			R/S lesion
15	63	M	Y	Y	10.2	<0.5		NS	N	Y			normal
16	46	M	Y	Y	17	<0.5		NS	N	Y			normal
17	33	F	Y	Y	10.2	0.6	18	Ns	Y	Y	7.88	R/S	normal
18	48	M	Y	N	28.4	0.32	88.8	Ns	N	Y			normal
19	49	F	Y	Y	11.6	0.67	17.3	NS	N	Y			normal
20	58	M	Y	N	27.5	0.07	330	NS	Y	Y	0.29	R/S	R/S
21	34	F	Y	Y	12.6	0.57	22.1	NS	Y	Y	4.6	R/S	L/S
22	73	M	Y	Y	57.3	<0.5		NS	N	Y			L/S lesion
23	33	M	Y	Y	10.2	0.6	17	NS	Y	Y	7.88		normal
24	47	F	Y	Y	40.2	0.11		NS	Y	Y	0.47	R/S	normal
25	50	F	Y	Y	26.5	0.9	29.2	NS	N	Y		L/S	R/S lesion
26	54	M	Y	Y	37.3	2.0	18.6	NS	N	Y			R/S lesion
27	70	M	Y	Y	24	0.2	120	NS	N	Y			normal
28	50	M	Y	Y	32	1.9		NS	N	Y			R/S lesion
29	39	F	Y	Y	28.1	0.25	112	NS	N	Y			L/S lesion
30	64	M	Y	Y	22.8	0.16	143	NS	Y	N			L/S lesion
31	47	M	Y	Y	28.4	0.3	88.8	NS	N	Y			normal
32	60	M	Y	Y	30	<0.5	>60	Ns	N	Y			normal

et al., and William Young et al. It appears that a cut-off of ≤0.5 is reliable for avoiding the misclassification of bilateral disease as contralateral unilateral disease. This cut-off value performed well in identifying either left or right unilateral disease.[6,7]

The limitation of this single-centre study is the generalizability of its results to other centres performing AVS, mainly due to differences in procedural technique, cosyntropin infusion use, and aldosterone and cortisol assays. Stimulated AVS was not routinely available in Sri Lanka, except for patients who could afford cosyntropin, owing to the economic crisis. Furthermore, the outcomes were based on the retrospective analysis.

The main strength of our study is that its results were derived from a well-defined national cohort. Patient management was standardized according to the Endocrine Society clinical guidelines whenever feasible, and we used the LI and cut-off values recommended by the most recent Endocrine Society guidelines, which have been shown to be most reliable. Nonetheless, this is the first study reporting the effectiveness of AVS in the management of PA from Sri Lanka.

CONCLUSION

The high diagnostic accuracy of AVS compared to imaging studies further supports the suggestion that AVS should serve as the gold standard diagnostic test for the subtyping of PA. Furthermore, successful cannulation of both adrenal veins is critical for reliable subtype characterization.

Aknowledgments
The authors acknowledge the medical laboratory scientists from the Department of Chemical Pathology at NHSL and MRI for their assistance in the laboratory analysis of cortisol and aldosterone samples.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CB: Conceptualization, Methodology, Writing – Original draft preparation; **SM:** Software, validation, Data curation; **SN:** Conceptualization, Methodology; **SO:** Investigations, resources; **JL:** Investigations, Resources; **GK:** Supervision, Writing – Reviewing and Editing.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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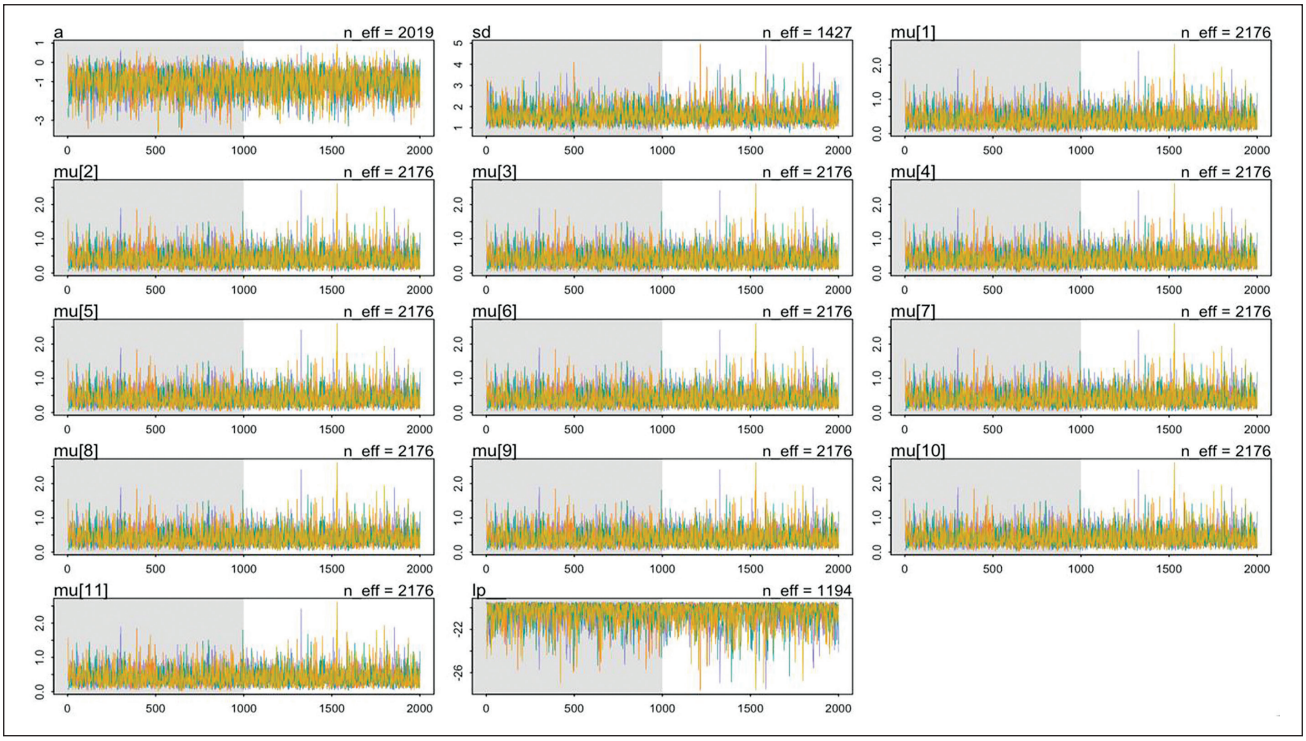
SUPPLEMENTARY MATERIAL



Supplementary Figure. Trace plot of the parameter estimations of the grand intercept (a), standard deviation (sd) and the means of each of the observations (mu[1] to lp).