Kementerian Pendidikan, Kebudayaan, Riset dan Teknologi
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PROPOSAL PENELITIAN 2023
Rencana Pelaksanaan Penelitian: tahun 2023 s.d. tahun 2024

1. JUDUL PENELITIAN

Perancangan alat deteksi genotyping HPV berbasis multiplex recombinase polymerase amplification dan nucleic acid lateral flow immunoassay (mRPA- NALFIA) sebagai alternatif metode PCR skrining kanker serviks yang mudah dan murah di fasilitas kesehatan primer

Bidang Fokus RIRN / Bidang Unggulan Perguruan Tinggi	Tema	Topik (jika ada)	Rumpun Bidang Ilmu
Kesehatan	Teknologi alat kesehatan dan diagnostik	Pengembangan in vivo diagnostic (IVD) untuk deteksi penyakit degenerative	Ilmu Biomedik

Kategori (Kompetitif Nasional/ Desentralisasi/ Penugasan)	Skema Penelitian	Strata (Dasar/ Terapan/ Pengembangan)	SBK (Dasar, Terapan, Pengembangan)	Target Akhir TKT	Lama Penelitian (Tahun)
Penelitian Kompetitif Nasional	Penelitian Fundamental - Reguler	Riset Dasar	SBK Riset Dasar	3	2

2. IDENTITAS PENGUSUL

Nama, Peran	Perguruan Tinggi/ Institusi	Program Studi/ Bagian	Bidang Tugas	ID Sinta
RADITYA WRATSANGKA Ketua Pengusul	Universitas Trisakti	Profesi Dokter	Koodinasi pengumpulan sampel dan uji alat di lapangan	5989166
MONICA DWI HARTANTI Anggota Pengusul	Universitas Trisakti	Pendidikan Dokter	Koordinasi analisis sampel di laboratorium	6679344
TJHWA ENDANG DJUANA Anggota Pengusul	Universitas Trisakti	Teknik Elektro	koordinasi analisis data in silico terkait genotyping HPV	5993185
ALVIONITA KOGOYA Anggota Pengusul	Universitas Trisakti	Pendidikan Dokter	Membantu uji sampel di laboratorium	-
Dr. dr Christina Safira	Pusat Riset	-	Membantu	-

Nama, Peran	Perguruan Tinggi/ Institusi	Program Studi/ Bagian	Bidang Tugas	ID Sinta
Whinie Lestari, M.Kes Anggota Pengusul	Biomedis, Badan Riset dan Inovasi Nasional		pengembangan alat deteksi genotyping HPV	
Drh. Didik Tulus Subekti, M.Kes Anggota Pengusul	Pusat Riset Biomedis, Badan Riset dan Inovasi Nasional	-	Koordinasi pengembangan alat deteksi genotyping HPV	-
Dr. Sunarno, M.Si.Med Anggota Pengusul	Pusat Riset Biomedis, Badan Riset dan Inovasi Nasional	-	Membantu uji sampel di laboratorium	-

3. MITRA KERJASAMA PENELITIAN (JIKA ADA)

Pelaksanaan penelitian dapat melibatkan mitra kerjasama yaitu mitra kerjasama dalam melaksanakan penelitian, mitra sebagai calon pengguna hasil penelitian, atau mitra investor

Mitra	Nama Mitra	Dana

4. LUARAN DAN TARGET CAPAIAN

Luaran Wajib

Tahun Luaran	Kategori Luaran	Jenis Luaran	Status target capaian	Keterangan
1	Artikel di Jurnal	Artikel di Jurnal Internasional Terindeks di Pengindeks Bereputasi	accepted/published	PeerJ
2	Kekayaan Intelektual (KI)	Paten Sederhana	terdaftar	Alat deteksi genotyping HPV berbasis mRPA-NALFIA

5. ANGGARAN

Rencana Anggaran Biaya penelitian mengacu pada PMK dan buku Panduan Penelitian dan Pengabdian kepada Masyarakat yang berlaku.

Total RAB 2 Tahun Rp. 528.018.420,00

Tahun 1 Total Rp221.100.000,00

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	Primer PCR	Unit	12	350.000	4.200.000
Bahan	Bahan Penelitian (Habis Pakai)	Kit Miniprep DNA 200 reaksi	Unit	2	11.000.000	22.000.000
Bahan	Bahan Penelitian (Habis Pakai)	TwistDX	Unit	3	17.000.000	51.000.000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	MyTaq Master Mix 1000 reaction	Unit	1	4.750.000	4.750.000
Bahan	Bahan Penelitian (Habis Pakai)	Agarose Powder	Unit	1	1.750.000	1.750.000
Bahan	Bahan Penelitian (Habis Pakai)	Sybr safe DNA Stain	Unit	2	2.750.000	5.500.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen pippet tips 0.5 - 10 ul	Unit	10	450.000	4.500.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen pippet tips 100 ul	Unit	10	450.000	4.500.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen pippet tips 200 ul	Unit	10	475.000	4.750.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen pippet tips 1000 ul	Unit	10	500.000	5.000.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen Microtube 1.5 ml (500 pcs)	Unit	1	575.000	575.000
Bahan	Bahan Penelitian (Habis Pakai)	Axygen PCR tube 0.2 ml flat cap clear (500 pcs)	Unit	1	1.851.000	1.851.000
Bahan	Bahan Penelitian (Habis Pakai)	Pewarna digoxigenin labelling kit	Unit	1	8.503.200	8.503.200
Bahan	Bahan Penelitian (Habis Pakai)	Anti-Cy3 / Cy5 antibody	Unit	1	11.903.000	11.903.000
Bahan	Bahan Penelitian (Habis Pakai)	Anti-Fluorescein antibody	Unit	1	9.817.800	9.817.800
Analisis Data	Biaya analisis sampel	HPV genotyping	Unit	70	1.150.000	80.500.000

Tahun 2 Total Rp306.918.420,00

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Bahan	Bahan Penelitian (Habis Pakai)	Universal Lateral Flow Assay Kit	Unit	2	32.051.710	64.103.420
Pengumpulan Data	HR Pembantu Peneliti	Honor pembantu peneliti untuk pengumpulan data 1 orang x 4 jam x 10 hari x 4 bulan	OJ	160	25.000	4.000.000

Jenis Pembelanjaan	Komponen	Item	Satuan	Vol.	Biaya Satuan	Total
Analisis Data	Biaya analisis sampel	Genotyping HPV	Unit	125	1.600.000	200.000.000
Analisis Data	HR Pengolah Data	Pengolahan data penelitian	P (penelitian)	1	1.540.000	1.540.000
Analisis Data	HR Sekretariat/ Administrasi Peneliti	Honor administrasi analisis data penelitian 1 orang x 6 bulan	OB	6	300.000	1.800.000
Analisis Data	Biaya konsumsi rapat	Biaya konsumsi rapat makan dan snack 9 orang x 5 hari	OH	45	75.000	3.375.000
Analisis Data	Transport Lokal	Transport lokal 9 orang x 3 bulan x 5 kali	OK (kali)	135	150.000	20.250.000
Pelaporan, Luaran Wajib, dan Luaran Tambahan	Uang harian rapat di luar kantor	Rapat pembuatan laporan dan luaran 9 orang x 5 hari	OH	45	130.000	5.850.000
Pelaporan, Luaran Wajib, dan Luaran Tambahan	Luaran KI (paten, hak cipta dll)	Hak paten sederhana	Paket	1	3.000.000	3.000.000
Pelaporan, Luaran Wajib, dan Luaran Tambahan	Biaya penyusunan buku termasuk book chapter	Pembuatan monograf	Paket	1	3.000.000	3.000.000

6. KEMAJUAN PENELITIAN

A. RINGKASAN

Latar belakang penelitian ini adalah masih rendahnya angka keberhasilan skrining kanker serviks sehingga membuat kanker serviks memiliki biaya pengobatan langsung tertinggi di Indonesia berdasarkan data BPJS. Metode skrining yang umumnya diterapkan adalah Pap Smear dan Inspeksi Visual Asam asetat (IVA), namun sensitivitas dan spesifisitas masih rendah, terutama untuk lesi prekanker. Kombinasi tes DNA- HPV direkomendasikan oleh WHO untuk meningkatkan keberhasilan skrining kanker serviks, namun diperlukan reagen dan alat yang mahal sehingga sulit diterapkan di fasilitas kesehatan primer. Metode Recombinase Polimerase Amplification merupakan uji isotermal dengan suhu tunggal 37-42°C sehingga dipercaya dapat menggantikan metode PCR sebagai point of care test. Hasil amplifikasi dapat divisualisasikan dengan perangkat elektroforesis maupun metode nucleic acid lateral flow immunoassay (NALFIA). Elektroforesis dan NALFIA telah banyak dikombinasikan dengan metode PCR namun metode RPA umumnya menggunakan metode elektroforesis untuk visualisasi sehingga membutuhkan waktu sekitar 3 jam. Tujuan penelitian ini membuat purwarupa alat deteksi HPV tipe 16, 18 dan 52 dengan metode mRPA- NALFIA dengan sensifititas dan spesifisitas yang mendekati metode PCR sehingga dapat menjadi alternatif metode PCR yang mudah dan murah di fasilitas kesehatan primer.

Penelitian ini berlangsung selama 2 tahun. Sesuai dengan target TKT 3 pada akhir kegiatan penelitian selama dua tahun, maka pada tahun pertama saat ini kegiatan terfokus pada desain dan pengembangan metode dan formulasi mRPA-NALFIA, yang terbagi dalam 4 tahap, yaitu desain algoritma dan seleksi primer mRPA; evaluasi kondisi reaksi mRPA; evaluasi primer mRPA dengan PCR dan persiapan template DNA; dan modifikasi protokol PCR dan mRPA dengan primer berlabel.

Target luaran penelitian ini adalah publikasi di jurnal internasional Q1 PeerJ dan Hak Cipta buku saku penelitian. Hasil penelitian yang sudah diperoleh mencapai 97 %, termasuk artikel dengan status submit pada jurnal PeerJ dan Sertifikat Hak Cipta Buku Saku Penelitian. Kami telah berhasil menemukan protokol mRPA yang untuk tipe HPV 16 dan 52, dan kami optimis finalisasi suhu optimal RPA untuk tipe HPV 18 akan segera terealisasi. Protokol mRPA untuk ketiga tipe HPV yang diperoleh pada penelitian tahun pertama dibutuhkan sebagai data dasar kelanjutan penelitian dan pembuatan purwarupa mRPA-NALFIA pada tahun kedua.

B. KATA KUNCI

Kanker serviks; HPV; mRPA; NALFIA; PCR

Pengisian poin C sampai dengan poin H mengikuti template berikut dan tidak dibatasi jumlah kata atau halaman namun disarankan seringkas mungkin. Dilarang menghapus/memodifikasi template ataupun menghapus penjelasan di setiap poin.

C. **HASIL PELAKSANAAN PENELITIAN:** Tuliskan secara ringkas hasil pelaksanaan penelitian yang telah dicapai sesuai tahun pelaksanaan penelitian. Penyajian meliputi data, hasil analisis, dan capaian luaran (wajib dan atau tambahan). Seluruh hasil atau capaian yang dilaporkan harus berkaitan dengan tahapan pelaksanaan penelitian sebagaimana direncanakan pada proposal. Penyajian data dapat berupa gambar, tabel, grafik, dan sejenisnya, serta analisis didukung dengan sumber pustaka primer yang relevan dan terkini.

Sesuai dengan proposal yang disetujui, penelitian ini bertujuan untuk:

1. Pengembangan protokol yang meliputi desain primer mRPA yang spesifik untuk gen L1, E6 dan E7 HPV tipe 16, 18 dan 52 dan penentuan kondisi optimal reaksi mRPA dan NALFIA.
2. Pengujian klinis alat rancangan untuk menilai keakuratan, sensitivitas, dan spesifisitas metode yang diusulkan pada sampel yang representatif.

Pada tahun pertama penelitian ini, pelaksanaan penelitian difokuskan kepada desain alogritma dan pengembangan metode dan formulasi mRPA-NALFIA. Pelaksanaan tersebut berlangsung dalam tahap-tahap beserta realisasinya seperti tercantum pada Tabel 1.

Tabel 1. Tahapan pelaksanaan penelitian sampai saat ini

No.	Aktivitas	Bukti Luaran	Target Indikator Capaian	Realisasi
1	Desain algoritma dan seleksi primer mRPA	Primer yang siap digunakan	Tersedia	100 %
2	Modifikasi protokol PCR dan optimasi kondisi reaksi mRPA	Protokol PCR dan reaksi mRPA yang siap digunakan	Tersedia	100 %
3	Evaluasi primer mRPA dengan PCR dan persiapan template DNA	Primer mRPA dan template DNA yang siap digunakan	Tersedia	100 %
4	Modifikasi dan uji protokol PCR dan mRPA dengan primer berlabel	PCR dan mRPA dengan primer berlabel memiliki hasil yang sama dengan primer tanpa label	Tersedia	97 %

Hasil dari masing-masing tahapan tertuang di bawah ini.

1. **Desain algoritma dan seleksi primer mRPA**

   Target deteksi tipe HPV DNA adalah tipe 16, 18 dan 52, berdasarkan hasil analisis data RISKESDAS 2018. Kami menggunakan sekuens L1, E6 dan E7 HPV tipe 16, 17 dan 52,

untuk mendesain dan menseleksi primer mRPA yang akan digunakan berdasarkan database sekuense gen yang ada di NCBI. Hasil pencarian tertera pada Tabel 2.

Tabel 2. Hasil pencarian sekuens target HPV tipe 16, 18 dan 52 dari database NCBI

No	Tipe HPV	Target	Jumlah sekuens	Panjang sekuens (bp)
1	16	L1	338	1518
		E6	69	477
		E7	73	297
2	18	L1	112	1707
		E6	9	477
		E7	3	318
3	52	L1	23	1590
		E6	26	447

Hasil alignment masing-masing target pada ketiga tipe HPV menunjukkan sebagian besar memiliki daerah yang conserved. Daerah *conserved* ditunjukkan dengan tanda * (Gambar 1).

```
CLUSTAL O(1.2.4) multiple sequence alignment

lcl|KC662605.1_cds_AGM34461.1_1      ATGTATGGACCTAAGGCAACATTGCAAGACATTGTATTGCATTTAGAGCCTCAAAATGAA      60
lcl|KC456641.1_cds_AGG40788.1_1      ATGTATGGACCTAAGGCAACATTGCAAGACATTGTATTGCATTTAGAGCCTCAAAATGAA      60
lcl|KC662604.1_cds_AGM34460.1_1      ATGCATGGACCTAAGGCAACATTGCAAGACATTGTATTGCATTTAGAGCCCCAAAATGAA      60
                                     *** ********************************************** *********

lcl|KC662605.1_cds_AGM34461.1_1      ATTCCGGTTGACCTTCTATGTCACGAGCAATTAAGCGACTCAGAGGAAGAAAACGATGAA      120
lcl|KC456641.1_cds_AGG40788.1_1      ATTCCGGTTGACCTTCTATGTCACGAGCAATTAAGCGACTCAGAGGAAGAAAACGATGAA      120
lcl|KC662604.1_cds_AGM34460.1_1      ATTCCGGTTGACCTTCTATGTCACGAGCAATTAAGCGACTCAGAGGAAGAAAACGATGAA      120
                                     ************************************************************

lcl|KC662605.1_cds_AGM34461.1_1      ATAGATGGAGTTAATCATCAACATTTACCAGCCCGACGAGCCGAACCACAACGTCACACA      180
lcl|KC456641.1_cds_AGG40788.1_1      ATAGATGGAGTTAATCATCAACATTTACCAGCCCGACGAGCCGAACCACAACGTCACACA      180
lcl|KC662604.1_cds_AGM34460.1_1      ATAGATGGAGTTAATCATCAACATTTACCAGCCCGACGAGCTGAACCACAACGTCACACA      180
                                     ************************************** ******************

lcl|KC662605.1_cds_AGM34461.1_1      ATGTTGTGTATGTGTTGTAAGTGTGAAGCCAGAATTGAGCTAGTAGTAGAAAGCTCAGCA      240
lcl|KC456641.1_cds_AGG40788.1_1      ATGTTGTGTATGTGTTGTAAGTGTGAAGCCAGAATTGAGCTAGTAGTAGAAAGCTCAGCA      240
lcl|KC662604.1_cds_AGM34460.1_1      ATGTTGTGTATGTGTTGTAAGTGTGAAGCCAGAATTGAGCTAGTAGTAGAAAGCTCAGCA      240
                                     ************************************************************

lcl|KC662605.1_cds_AGM34461.1_1      GACGACCTTCGAGCATTCCAGCAGCTGTTTCTGAGCACCCTGTCCTTTGTGTGTCCGTGG      300
lcl|KC456641.1_cds_AGG40788.1_1      GACGACCTTCGAGCATTCCAGCAGCTGTTTCTGAGCACCCTGTCCTTTGTGTGTCCGTGG      300
lcl|KC662604.1_cds_AGM34460.1_1      GACGACCTTCGAGCATTCCAGCAGCTGTTTCTGAACACCCTGTCCTTTGTGTGTCCGTGG      300
                                     ********************************** ************************

lcl|KC662605.1_cds_AGM34461.1_1      TGTGCATCCCAGCAGTAA 318
lcl|KC456641.1_cds_AGG40788.1_1      TGTGCATCCCAGCAGTAA 318
lcl|KC662604.1_cds_AGM34460.1_1      TGTGCATCCCAGCAGTAA 318
                                     ******************
```

Gambar 1. Hasil alignment gen E7 HPV tipe 18 dengan menggunakan Clustal W [1]

Daerah *conserved* tersebut merupakan target desain primer untuk masing-masing gen L1, E6 dan E7 pada HPV tipe 16, 18 dan 52. Kandidat primer kemudian diblast dengan menggunakan BLASTN pada web NCBI [2]. Hasil yang didapat terangkum pada Tabel 3.

Tabel 3. Hasil kandidat primer yang akan digunakan

Virus	Target Gen	Sekuens (5′ - 3′)
HPV-16	L1	ATA GTT CCA GGG TCT CCA
		AGT CCA TAG CAC CAA AGC
	L1	GAA CAC TGG GGC AAA GGA TC
		TAC AAT GAA TAA CCA CAA CA
	L1	TTT GGT CTA CAA CCT CCC CCA GGA
		TTC TTT AGG TGC TGG AGG TGT ATG
	E6	TCA AAA GCC ACT GTG TCC TGA
		CGT GTT CTT GAT GAT CTGCAA
	E6/E7	GTC AAA AGC CAC TGT GTC CT
		CCA TCC ATT ACA TCC CGT AC
HPV-18	E6/E7	CGACAGGAACGACTCCAACGA
		GCTGGTAAATGTTGATGATTAACT
	E6/E7	CCGAGCACGACAGGAACGACT
		TCGTTTTCTTCCTCTGAGTCGCTT
	L1	CCTTGGACGTAAATTTTTGG
		CACGCACACGCTTGGCAGGT
HPV-52	L1	GCTGAGGTTAAAAAGGAAAGC
		ATGCAGACGGTGGTGGGGTAAGG
	E6/E7	GGT GTT GGT GCT GGT GCT TTT GCT A
		CAG TTA CAG GGG GAC GAA TGG TGG A

2. Modifikasi protokol PCR dan optimasi kondisi reaksi mRPA

Reaksi PCR sebanyak 50 µl, terdiri dari 25 µl myTaq HS Red Mix, 21 µl ddH2O, 1 µl primer forward dan 1 µl primer reverse 20 µM, beserta 2 µl DNA (200 ng).

Kondisi PCR yang digunakan untuk HPV tipe 16, 18 dan 52 adalah sebagai berikut:

- Denaturasi awal dengan suhu 95°C selama 15 menit
- Siklus PCR sebanyak 35 siklus yang terdiri dari:
    - 94°C selama 45 detik
    - 54°C selama 45 detik (HPV tipe 16); 51°C selama 30 detik (HPV tipe 18); 53°C selama 30 detik (HPV tipe 52)
    - 72°C selama 60 detik serta
- Elongasi akhir pada suhu 72°C selama 7 menit.

Reaksi mRPA sebanyak 25 µL diinkubasi selama 30 menit pada suhu 39°- 40°C. Untuk mengevaluasi kondisi reaksi mRPA, diperlukan penentuan konsentrasi minimal primer yang dihasilkan amplikon gen L1 dan E6/E7, serta waktu inkubasi terpendek dengan batas deteksi tertinggi dan spesifisitas yang benar. Konsentrasi primer yang digunakan adalah 10 µM untuk masing-masing primer forward dan reverse.

3. Evaluasi primer mRPA dengan PCR dan persiapan template DNA

Isolasi DNA telah dilakukan dalam rangka persiapan tempalte DNA pada 37 sampel swab serviks yang tersimpan dengan karakteristik subyek yang dirangkum pada Tabel 4.

Tabel 4. Karakteristik subyek penelitian

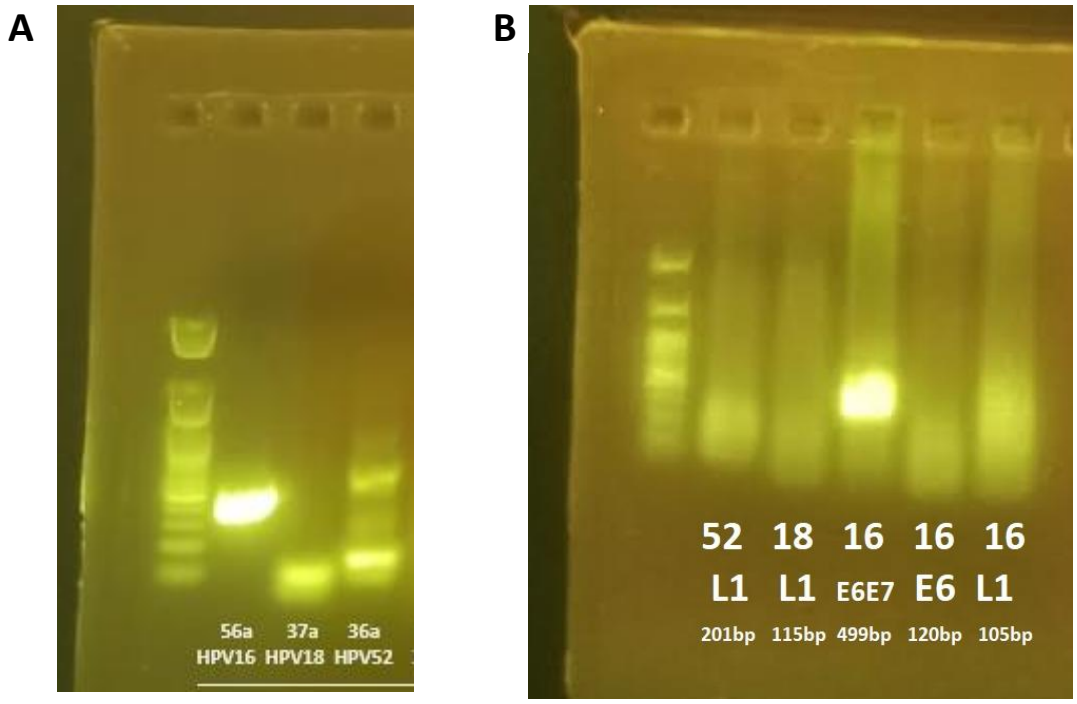
Karakteristik	Jumlah
Usia	
25 - 34	3
35 - 44	8
45 - 50	9
> 50	12
HPV genotyping	
Tidak ditemukan	13
Tipe High Risk	18
Tipe Low Risk	1
Tipe HPV Genotyping High Risk	
52	6
18	3
35	1
59	2
45	1
73	1
16	4
58	1
66	1
68	1
Tipe HPV Genotyping Low Risk	
26	1
84	1

Sampel klinis yang terkonfirmasi memiliki HPV tipe 16, 18 dan 52 menjadi sampel positif pada tahap ini.

Primer tanpa label dari hasil seleksi primer mRPA dievalusi dengan PCR. Reaksi PCR sesuai dengan optimasi langkah sebelumnya dipersiapkan beserta 2 µl DNA (200 ng) dengan total reaksi 50 µl. Kondisi PCR yang digunakan untuk tiap tipe HPV juga menggunakan kondisi PCR hasil optimasi sebelumnya.

Hasil optimasi PCR dan mRPA divisulisasi dan dianalisis dengan elektroforesis gel agarosa 1% pada alat blue light transiluminator. Ukuran amplicon untuk PCR dan RPA L1 dan E6/7

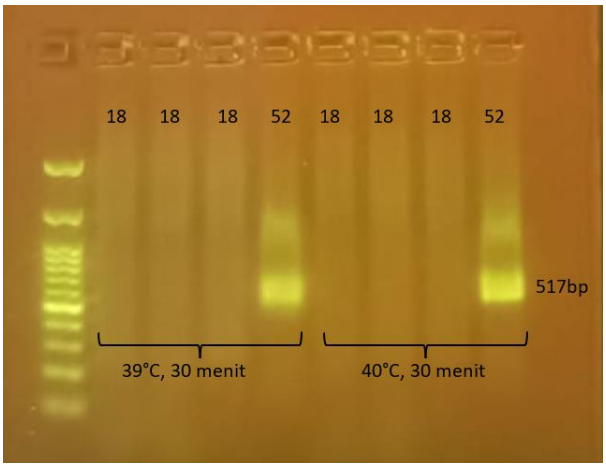
berkisar antara 105 bp – 499 bp.



Gambar 2. Hasil elektroforesis PCR (A) dan RPA (B). Sampel positif kontrol yang digunakan adalah sampel swab serviks DNA yang positif HPV 16, 18 dan 52.

Hasil yang didapatkan adalah terlihatnya pita DNA dengan ukuran yang sesuai untuk tipe HPV 16 (499 bp), HPV 18 (115 bp) dan HPV 52 (201 bp) pada metode PCR. Untuk RPA, pita DNA yang sesuai hanya terobservasi pada HPV 16 (499 bp).

Untuk mendapatkan hasil pita DNA HPV tipe 18 dan 52 pada metode RPA, maka digunakan pasangan primer lain. Hasil elektroforesis menunjukkan bahwa HPV tipe 52 dapat tervisualisasi pada gel elektroforesis dengan baik.



Gambar 3. Hasil RPA HPV 18 dan 52 pada elektroforesis.

4. Modifikasi protokol PCR dan mRPA dengan primer berlabel

Primer berlabel yang digunakan pada tahapan ini adalah primer *forward* berlabel digoxigenin pada ujung 5' untuk kesepuluh pasang primer. Adapun primer *reverse* dilabel dengan FAM pada ujung 3' dari masing-masing pasang primer. Langkah ini dilakukan untuk menguji apakah protokol PCR dengan primer berlabel akan menghasilkan hasil yang sama dengan primer tanpa label yang telah didesain sebelumnya. Produk amplikon dengan ukuran yang sesuai dianalisis melalui elektroforesis gel agarosa 1%. Untuk persiapan template DNA HPV L1 (dan E6/E7) sebagai representasi HPV tipe 16, 18 dan 52, primer PCR yang melingkupi wilayah amplifikasi RPA akan digunakan. Kondisi PCR serupa dengan yang telah disebutkan sebelumnya, kecuali suhu perpanjangan dan ukuran produk yang akan disesuaikan. Produk PCR dipurifikasi dengan agarosa dan diukur kuantitasnya.

D. **STATUS LUARAN**: Tuliskan jenis, identitas dan status ketercapaian setiap luaran wajib dan luaran tambahan (jika ada) yang dijanjikan. Jenis luaran dapat berupa publikasi, perolehan kekayaan intelektual, hasil pengujian atau luaran lainnya yang telah dijanjikan pada proposal. Uraian status luaran harus didukung dengan bukti kemajuan ketercapaian luaran sesuai dengan luaran yang dijanjikan. Lengkapi isian jenis luaran yang dijanjikan serta mengunggah bukti dokumen ketercapaian luaran wajib dan luaran tambahan melalui BIMA.

Aktivitas	Bukti Luaran	Target Indikator Capaian	Realisasi
Pembuatan laporan lengkap dan luaran	Bukti submit dan manuscript yang dapat diakses pada link berikut: https://drive.google.com/file/d/1wQkXw7E8SSeFOBOb4kpnssfoUJ7G9yKa/view?usp=drive_link	Published	Selesai 80%, status submitted
	Sertifikat hak cipta dan buku saku dapat diakses pada link berikut: https://drive.google.com/file/d/1hy_-36hmRyoHqG4bmzbVNNmn-cSCWk9s/view?usp=drive_link	Sertifikat terbit	100 %
	Video penelitian dapat diakses pada link berikut: https://drive.google.com/file/d/1ewzL3oFWLIdsm_eZ6uiu1EHhihwnu8E4/view?usp=sharing	Video ada	100 %

E. **PERAN MITRA:** Tuliskan realisasi kerjasama dan kontribusi Mitra baik *in-kind* maupun *in-cash* (untuk Penelitian Terapan, Penelitian Pengembangan, PTUPT, PPUPT serta KRUPT). Bukti pendukung realisasi kerjasama dan realisasi kontribusi mitra dilaporkan sesuai dengan kondisi yang sebenarnya. Bukti dokumen realisasi kerjasama dengan Mitra diunggah melalui BIMA.

Penelitian ini tidak memiliki mitra seperti tercantum pada proposal.

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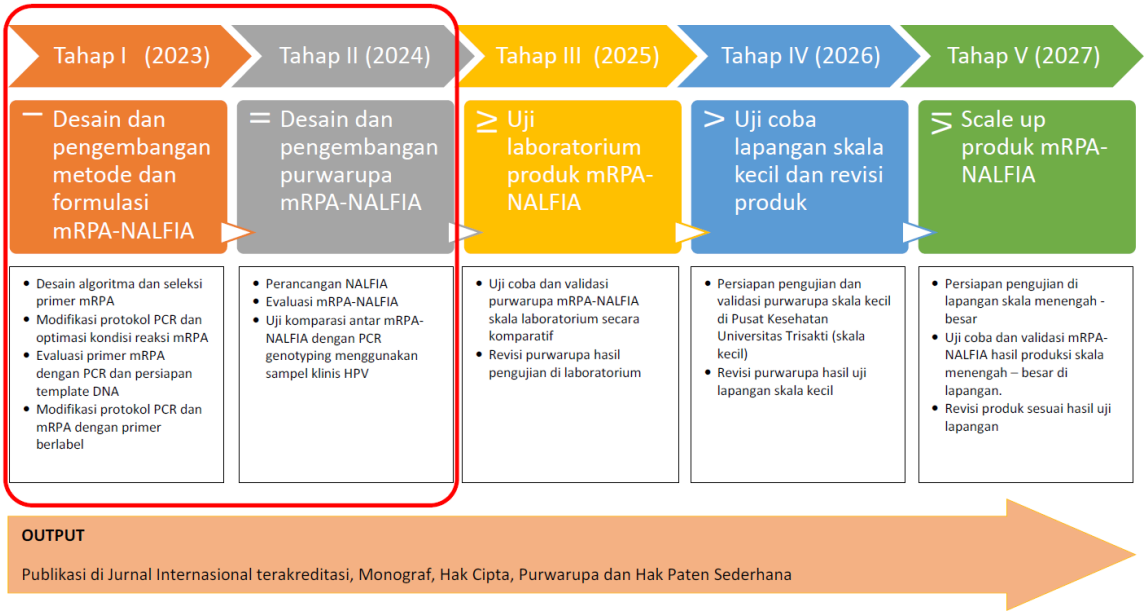
Penelitian tahun kedua (2024) akan dilaksanakan kegiatan sebagai berikut:

No.	Aktivitas	Target Indikator Capaian	Rencana Realisasi	Rencana Penyelesaian
1	Modifikasi dan uji protokol PCR dan mRPA dengan primer berlabel	Tersedia	100 %	Finalisasi protokol mRPA dengan primer berlabel untuk HPV tipe 18 dan 52
3	Publikasi di jurnal internasional terindex SCOPUS Q1 PeerJ	Published	100 %	Revisi manuscript jika dibutuhkan
4	Perancangan NALFIA	Tersedia	100 %	Hasil mRPA dapat divisualisasikan pada NALFIA
5	Uji komparasi antar mRPA-NALFIA dengan PCR genotyping menggunakan sampel klinis HPV	Published	100 %	Sensifivitas dan sensitivitas mRPA-NALFIA sesuai dengan PCR genotyping
6	Purwarupa alat deteksi HPV tipe 16, 18 dan 52 dengan metode mRPA-NALFIA	Tersedia	100 %	Pembuatan purwarupa
7	Monograf	Terbit dengan ISBN	100 %	Pembuatan monograf
8	Hak paten sederhana	Terdaftar	100 %	Pengumpulan dan penulisan berkas-berkas untuk pengajuan hak paten sederhana

Penelitian ini adalah riset dasar yang dalam rangka pengembangan inovasi alat deteksi HPV dengan metode mRPA-NALFIA sebagai alternatif metode PCR di fasilitas kesehatan primer seperti yang tertuang pada peta jalan berikut di bawah ini.



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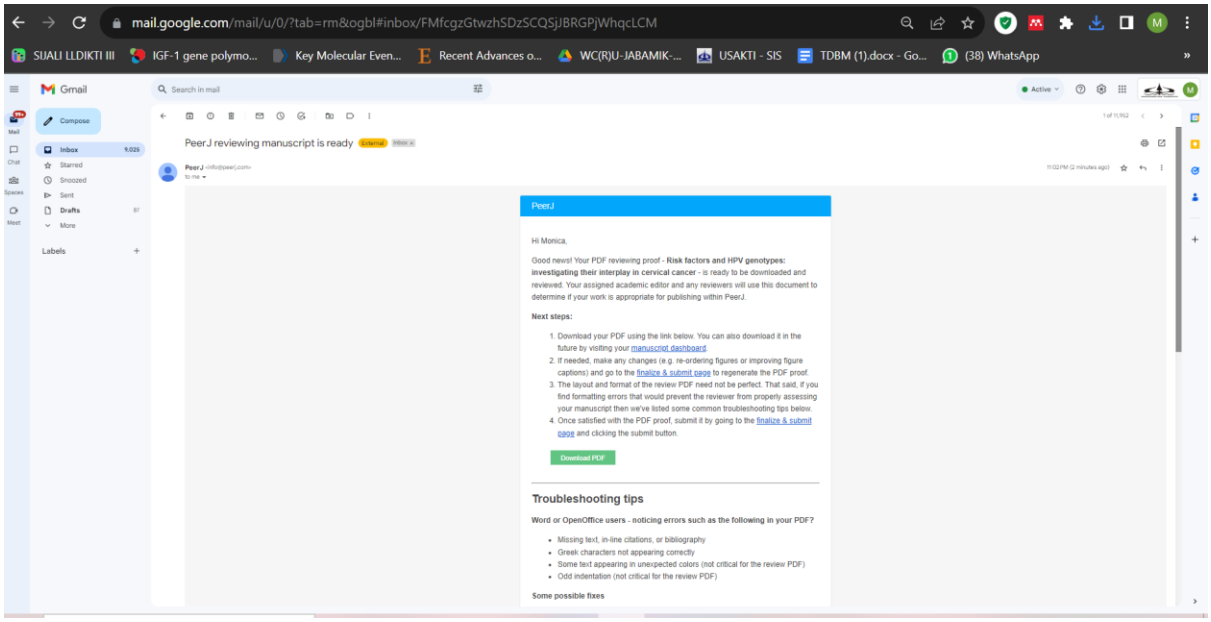
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Miranti Putri Aulia
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Risk factors and HPV genotypes: investigating their interplay in cervical cancer

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cancer management and prevention.

Risk factors and HPV genotypes: investigating their interplay in cervical cancer

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Abstract

Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to Human Papillomavirus (HPV) infection. This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients, providing insights into the multifaceted aspects of patient traits and their potential influence on the advancement of the disease. Women diagnosed with cervical cancer were recruited for this cross-sectional study. Cervical swabs were collected, and HPV genotypes were analyzed. Various risk factors were assessed through a questionnaire, which included age, age at marriage, age at first pregnancy, parity, smoking habits, contraceptive history, and the stage of cervical cancer diagnosis. Statistical analysis was conducted using the Chi-square or Fisher test, with a significance threshold set at $p<0.05$. The results indicated that HPV type 52 was the most prevalent among the high-risk HPV types, followed by HPV types 16 and 18. Notably, there were no significant correlations observed between these patient characteristics and HPV genotyping in cervical cancer patients ($p>0.05$). In conclusion, while we observed variations in patient traits, including age at marriage, age at first pregnancy, parity, smoking habits, and contraceptive history, these differences did not translate into statistically significant associations with specific HPV genotypes. Despite the multifaceted nature of patient characteristics, this study did not identify significant relationships between risk factors and HPV genotyping in cervical cancer patients. Further research is warranted to explore deeper into the complex interplay between these variables and their potential impact on disease progression. Understanding these nuances can contribute to more personalized approaches to cervical cancer management and prevention.

Keywords: Cervical cancer, HPV genotypes, Risk Factors, Indonesia

INTRODUCTION

Cervical cancer stands as a significant global health issue, ranking as the fourth most prevalent malignancy among women worldwide. According to data from the World Health Organization (WHO) in 2020, approximately 604,000 new cases and 342,000 deaths from cervical cancer were reported, with approximately 90% occurring in low-middle-income countries (World Health Organization, 2022). The global incidence ranges from 75 to 10 cases per 100,000 women (World Health Organization, 2020). Indonesia, as of 2012 data, recorded 20,928 cases of cervical cancer with 9,498 associated deaths (World Health Organization, 2022). World Health Organization (WHO) merekomendasikan tes DNA-HPV sebagai metode skrining yang utama pada tahun 2021(World Health Organization, 2021),

Cervical cancer is preventable, with Human Papillomavirus (HPV) infection being a crucial etiological factor. HPV is present in over 95% of cervical cancer lesions. While there's no direct treatment for the virus, some topical microbicides have shown intrinsic antiviral activity (Calagna et al., 2020). Although most HPV infections are asymptomatic and can resolve on their own, persistent HPV infection poses a risk of developing into precancerous lesions, ultimately leading to cervical cancer (Capra et al., 2017). High-risk HPV types, notably HPV 16 and 18, are responsible for low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) in the cervix. Timely identification and treatment of precancerous lesions can prevent progression (Ministry of Health Republic of Indonesia, 2018). Vaccination, protecting individuals from HPV infection, has demonstrated success in reducing cervical cancer incidence in developed countries alongside regular screening for adult women. However, low-middle-income countries often face limitations in preventive facilities and access, leading to advanced-stage diagnoses (World Health Organization, 2022), as observed in Indonesia, where approximately 66.4% of patients are diagnosed at stages IIB-IVB (Ministry of Health Republic of Indonesia, 2018).

HPV belongs to the Papillomaviridae family, comprising over 200 genotypes. HPV infects the squamous epithelium of the skin and mucous membranes, categorizing it into cutaneous and mucosal types. In terms of cancer and pre-cancerous lesions, HPV is classified into high-risk types associated with malignancy and low-risk types linked to benign lesions (Burd, 2003).

HPV infection is one of the most common sexually transmitted infections worldwide, affecting both men and women. Global genital HPV infection prevalence ranges from 3.5% to 45% in men

and 2% to 44% in women, with similar transmission rates (Kombe Kombe et al., 2020). Most HPV infections in men are asymptomatic and resolve spontaneously, often causing no symptoms. Genital warts are the primary clinical manifestation of symptomatic HPV infection in men, typically benign. In women, while many acquire cervical HPV infections, most do not progress to cervical cancer (Bosco et al., 2021). The integration of HPV into the cell genome is a key factor in cervical cancer development. HPV symptoms may not appear until months or years after infection, making detection challenging until genital warts or cancerous lesions emerge, particularly in women (Hu et al., 2015).

Efforts to eliminate cervical cancer include the WHO's 90-70-90 target for 2030, which aims for 90% of young girls to receive full vaccination at age 15, 70% of women to undergo screening at 35 and 45 years, and 90% of women with cervical cancer to receive management, including recovery from pre-cancerous lesions and treatment for invasive cancer cases (World Health Organization, 2020). Indonesia has responded by planning an HPV vaccination program for female teenagers as part of its national vaccination initiatives. However, this program has yet to encompass the adult female population. To align with the government's goals of developing domestic diagnostic tools and expanding screening reach, it is crucial to create cost-effective, sensitive, and specific diagnostic reagents tailored to the high-risk HPV genotypes commonly found in the Indonesian population. This preliminary study aims to correlate risk factors in to HPV genotypes among women in Indonesia.

MATERIAL AND METHOD/ METHODOLOGY

Ethical Clearance

This study was approved by the ethical clearance committee of Faculty of Medicine, Universitas Indonesia, with ethical clearance number of KET-1262/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from subjects before enrolment.

Study Design and Population

This is a cross-sectional study, observing the relationship between risk factors and HPV genotyping among women in Indonesia. The study was conducted in 2022 in Cipto mangun kusumo National Hospital, Jakarta with the targeted participants of women aged 18-65 years old.

Only women who have signed the informed consent were included in this study. Women who have had a prior HPV vaccination or a treatment related to cervical cancer were excluded from this study.

Data Collection

Forty-one participants were recruited consecutively according to inclusion and exclution criterias. Questionnares were subjected to the participants, containing detailed questions related to marriage status, smoking, and parity status. For HPV genotyping, cervical swab was collected in thin prep container and kept in 4C fridge for genotyping analysis.

HPV Genotyping

DNA Extraction was subjected to cervical swab using QIAamp® DNA Blood mini kit (Qiagen, cat. 51104) according to the manufacture's protocol. Briefly, sample in pellet resuspension was added to mixture of Qiagen Protease (Proteinase K) and Buffer AL. After 10 min and 56°C incubation, ethanol 96-100% was added. The mixture was then transferred to the QIAamp Mini Spin Column and centrifuged at 6000 x g for 1 min. Buffer AW2 and AE were added separately after serial centrifugation at different speeds and time. The extracted DNA was then amplified, and the HPV was genotyped using reverse dot blot "flow-through" hybridization method with GeneFlow Human papillomavirus (HPV) array test kit (cat. 92007). This method can detect different high-risk HPV types, including 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 81 and 82; and HPV low risk types, including 6, 11, 26, 40, 42, 43, 44, 54, 55, 57, 61, 70, 71, 72, and 84.

Statistical Analysis

The data were subjected to analysis using Microsoft Excel 2018 (version 16.16.14). Categorical variables were summarized by presenting absolute values and percentages. For testing the correlation of risk factors and HPV genotyping, Chi-square or Fisher test were used accordingly. All statistical analyses were carried out utilizing Graph Pad version 9.0.0. A p-value (two-tailed) less than 0.05 was considered statistically significant.

RESULTS

This study highlights the characteristics of women with cervical cancer and correlates those characteristics to HPV genotyping. These findings illuminate the multifaceted nature of patient characteristics in the study, underscoring the endeavor to explore the correlations between risk factors and HPV genotyping in cervical cancer among Indonesian patients.

Characteristics of participants

The study emphasizes the significance of patient age. The age distribution varied, with a minor proportion in the 25-34 age group, while the majority were aged 35 or older. Age at marriage emerged as a noteworthy factor. Roughly 44.4% of patients were married before the age of 20, while about 55.6% married at an age older than 20. There was substantial variation in the age at which patients experienced their first pregnancy. Approximately 25% of patients had their initial pregnancy before the age of 20, and 75% experienced it between the ages of 20 and 35. Differences in the number of parities among patients were observed, with 11.1% categorized as nulliparous (never having given birth) and 88.9% classified as multiparous (having given birth more than once). Smoking habits exhibited significant variability among patients, with 10.3% identified as active smokers and 89.7% as non-smokers (Table 1).

Diagnostic data reflected the severity of cervical cancer in the patients. A minority received a pre-cancer diagnosis, while 50% were at stage 2, 23.1% at stage 3, and 3.84% at stage 4, indicating differing levels of severity. The patterns of contraceptive use were diverse, with 33.3% of patients not using contraception and 66.7% using contraceptive methods. The study unveiled a diversity of HPV infections. Around 53.7% had no detectable high-risk or low-risk HPV types, 43% had high-risk HPV types, and 2.4% had low-risk HPV types. Various high-risk HPV types were identified, with HPV type 16 in some patients and HPV type 18 in others, among others. Low-risk HPV type 26 was detected in approximately 5.3% of patients. Coinfections were found in three women, possesing HPV type 16 and 52; 18, 66 and 68; and 26 and 84.

Relationship between risk factors and HPV genotyping

The relationship between risk factors and HPV genotyping was analysed using Chi-square or Fisher test. All categories were adjusted according to the criteria of statistical analysis. Most

participants possed high-risk HPV were in the groups of >45 years of age, >20 years at the time of marriage and pregnancy, multiparous, not being a smoker, and using contraceptions. However, we did not observe any significant relationships between those factors and HPV genotyping (Table 2).

DISCUSSION

This study highlights the importance of internal and external factors to the types of HPV infected women. However, no significant association was found in every factor with high-risk HPV. Surprisingly, we found that HPV type 52 dominated the HPV types found in women with cervical cancer.

Most of participants who were infected with high-risk HPV were older than 45 years old. Age of patients is a critical factor in understanding the dynamics and persistence of HPV infection. A study shows that high-risk HPV infection will develop into cervical cancer mostly at the age of 40 years old (Burger et al., 2017). Young aged women have a higher likelihood of clearing HPV infections spontaneously, while older women may experience persistent infections (Huber et al., 2021). Supporting our results, a study found that HPV type 18 and 45 are more prevalent in young women (Kong et al., 2019), highlighting the importance of examining age distribution among HPV genotyping data to enhance our understanding about age-related patterns in HPV infections.

Contrary to our results, several studies show the increasing number of cervical cancer in women age 20 – 29 years old in UK annually up to 10% (Patel et al., 2012), under 30 years old in Taiwan (Lau et al., 2009) and younger than 30 years old in China (Li et al., 2013).

Age of marriage and pregnancy is closely related to high-risk HPV infection that leads to cervical cancer. Early exposure to HPV is mostly through sexual activity and increases the risk of infection, especially to HPV type 16, whereas multiple sexual partners can increase the risk of HPV type 18 infection (Itarat et al., 2019). However, we did not analyse this factor. The age of pregnancy has been linked to HPV infection. A study in China shows a significant increase in susceptibility of HPV infection in pregnant women older than 35 years (Luo et al., 2021). In agreement with our results, HPV type 52 is the most prevalent HPV type found in these group age pregnant women (Luo et al., 2021).

Smoking is believed to be responsible for the development of cervical cancer. Tobacco increases HPV replication, promotes E6 and E7 oncoprotein expressions, decreases the ability of immune systems to clear the HPV infection and also promotes DNA damage due to HPV infection (Aguayo et al., 2020). Moreover, prolonged smoking exposure is thought to be promote a persistence HPV infection (Ma* et al., 2023), leading to the development of cervical cancer.

The use of hormonal contraception has been linked to the development of cervical cancer. However, this has become a controversial topic due to inconsistency in research. We did not find any significant correlation between the use of contraception and HPV genotyping. Similar to our study, a literature study found no significant correlation between the use of oral contraception and the risk of cervical cancer (Gadducci et al., 2020). A study in Finland also showed that there were no association between the methods of contraception and high-risk HPV infection (Bergqvist et al., 2021). Our results suggest that the use of contraception is not likely to related to high-risk HPV infection, however, more further studies about the type and the length of contraception used, especially in younger women are needed to reveal the trend of increasing incindence of cervical cancer in this age group.

CONCLUSION

The type of high-risk HPV varies among women with cervical cancer with HPV type 52 being the major type of HPV infection. Risk factors are also varies among women with cervical cancer and it is unlikely associated with HPV genotyping. Further studies on various risk factors and HPV genotyping are needed, especially in young aged women to targetting an alternative preventive strategy in cervical cancer.

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Table 1(on next page)

Characteristics of participants

Characteristics	Total	Percentage
Age (years)		
25-34	3	7.3
35-44	11	26.8
45-50	11	26.8
>50	16	39
Age at marriage		
<20	12	44.4
>20	15	55.6
Age at pregnancy		
<20	7	25.0
20-35	21	75.0
Parity number		
Nulliparous	3	11.1
Multiparous	24	88.9
Smoking		
Yes	3	10.3
No	26	89.7
Cancer stadium		
Pre-Cancer	3	11.5
Stadium 1	3	11.5
Stadium 2	13	50.0
Stadium 3	6	23.1
Stadium 4	1	3.8
Contraception		

Yes	10	66.7
No	5	33.3
HPV genotyping		
No HPV	22	53.7
High-risk HPV	18	43.9
Low-risk HPV	1	2.4
HPV type		
16	3	15.8
18	4	21.1
26	1	5.3
35	1	5.3
45	1	5.3
52	5	26.3
58	1	5.3
59	2	10.5
73	1	5.3

1

2

Table 2(on next page)

Association of risk factors and HPV genotyping in women with cervical cancer

1

Risk Factors	No HPV/low-risk HPV	High-risk HPV	p value
Age (years)			
<45	6	5	0.373
>=45	8	13	
Age at marriage			
<20	1	7	1
>20	2	9	
Age at pregnancy			
<20	0	5	0.539
20-35	3	12	
Parity number			
Nulliparous	1	0	0.143
Multiparous	1	12	
Smoking			
Yes	0	3	1
No	3	14	
Contraception			
Yes	1	5	1
No	0	4	

2

3

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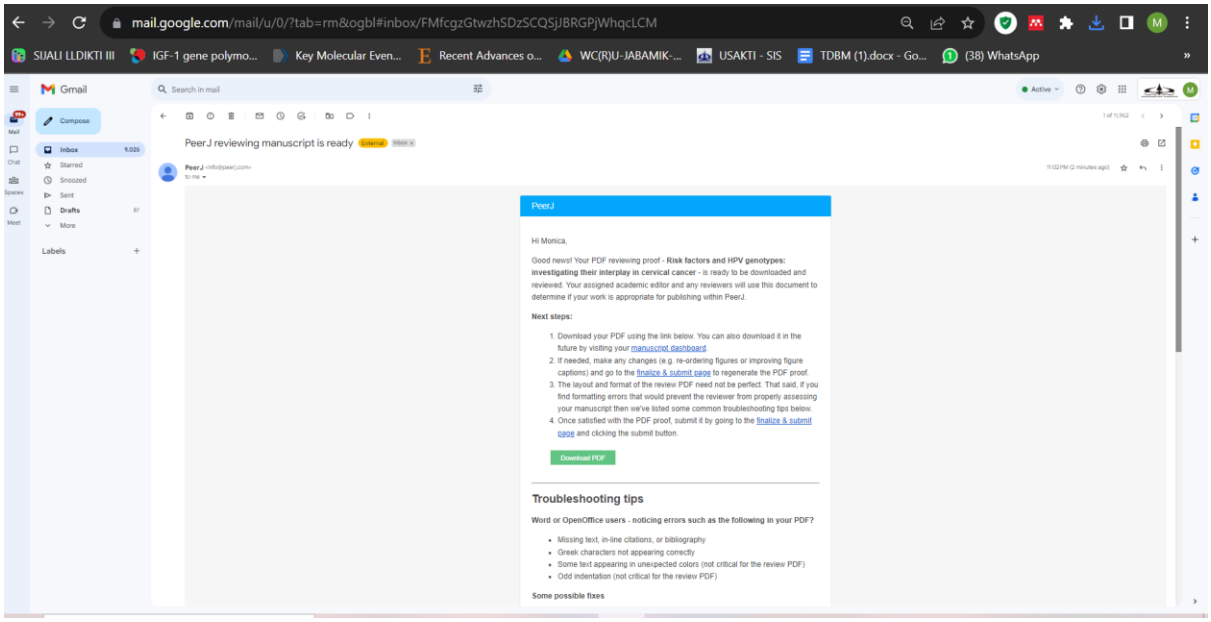
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KEYWORDS

Cervical cancerHPV genotypesRisk FactorsIndonesia

ABSTRACT

Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to Human Papillomavirus (HPV) infection. This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients, providing insights into the multifaceted aspects of patient traits and their potential influence on the advancement of the disease. Women diagnosed with cervical cancer were recruited for this cross-sectional study. Cervical swabs were collected, and HPV genotypes were analyzed. Various risk factors were assessed through a questionnaire, which included age, age at marriage, age at first pregnancy, parity, smoking habits, contraceptive history, and the stage of cervical cancer diagnosis. Statistical analysis was conducted using the Chi-square or Fisher test, with a significance threshold set at $p<0.05$. The results indicated that HPV type 52 was the most prevalent among the high-risk HPV types, followed by HPV types 16 and 18. Notably, there were no significant correlations observed between these patient characteristics and HPV genotyping in cervical cancer patients ($p>0.05$). In conclusion, while we observed variations in patient traits, including age at marriage, age at first pregnancy, parity, smoking habits, and contraceptive history, these differences did not translate into statistically significant associations with specific HPV genotypes.

and their potential impact on disease progression. Understanding these nuances can contribute to more personalized approaches to cervical cancer management and prevention.

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Risk factors and HPV genotypes: investigating their interplay in cervical cancer

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ABSTRACT

Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to Human Papillomavirus (HPV) infection. This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients, providing insights into the multifaceted aspects of patient traits and their potential influence on the advancement of the disease. Women diagnosed with cervical cancer were recruited for this cross-sectional study. Cervical swabs were collected, and HPV genotypes were analyzed. Various risk factors were assessed through a questionnaire, which included age, age at marriage, age at first pregnancy, parity, smoking habits, contraceptive history, and the stage of cervical cancer diagnosis. Statistical analysis was conducted using the Chi-square or Fisher test, with a significance threshold set at $p<0.05$. The results indicated that HPV type 52 was the most prevalent among the high-risk HPV types, followed by HPV types 16 and 18. Notably, there were no significant correlations observed between these patient characteristics and HPV genotyping in cervical cancer patients ($p>0.05$). In conclusion, while we observed variations in patient traits, including age at marriage, age at first pregnancy, parity, smoking habits, and contraceptive history, these differences did not translate into statistically significant associations with specific HPV genotypes.

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Risk factors and HPV genotypes: investigating their interplay in cervical cancer

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Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to Human Papillomavirus (HPV) infection. This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients, providing insights into the multifaceted aspects of patient traits and their potential influence on the advancement of the disease. Women diagnosed with cervical cancer were recruited for this cross-sectional study. Cervical swabs were collected, and HPV genotypes were analyzed. Various risk factors were assessed through a questionnaire, which included age, age at marriage, age at first pregnancy, parity, smoking habits, contraceptive history, and the stage of cervical cancer diagnosis. Statistical analysis was conducted using the Chi-square or Fisher test, with a significance threshold set at $p<0.05$. The results indicated that HPV type 52 was the most prevalent among the high-risk HPV types, followed by HPV types 16 and 18. Notably, there were no significant correlations observed between these patient characteristics and HPV genotyping in cervical cancer patients ($p>0.05$). In conclusion, while we observed variations in patient traits, including age at marriage, age at first pregnancy, parity, smoking habits, and contraceptive history, these differences did not translate into statistically significant associations with specific HPV genotypes. Despite the multifaceted nature of patient characteristics, this study did not identify significant relationships between risk factors and HPV genotyping in cervical cancer patients. Further research is warranted to explore deeper into the complex interplay between these variables and their potential impact on disease progression. Understanding these nuances can contribute to more personalized approaches to cervical

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Abstract

Cervical cancer continues to pose a substantial worldwide health challenge, primarily linked to Human Papillomavirus (HPV) infection. This research explores the complex relationship between various risk factors and the types of HPV detected in cervical cancer patients, providing insights into the multifaceted aspects of patient traits and their potential influence on the advancement of the disease. Women diagnosed with cervical cancer were recruited for this cross-sectional study. Cervical swabs were collected, and HPV genotypes were analyzed. Various risk factors were assessed through a questionnaire, which included age, age at marriage, age at first pregnancy, parity, smoking habits, contraceptive history, and the stage of cervical cancer diagnosis. Statistical analysis was conducted using the Chi-square or Fisher test, with a significance threshold set at $p<0.05$. The results indicated that HPV type 52 was the most prevalent among the high-risk HPV types, followed by HPV types 16 and 18. Notably, there were no significant correlations observed between these patient characteristics and HPV genotyping in cervical cancer patients ($p>0.05$). In conclusion, while we observed variations in patient traits, including age at marriage, age at first pregnancy, parity, smoking habits, and contraceptive history, these differences did not translate into statistically significant associations with specific HPV genotypes. Despite the multifaceted nature of patient characteristics, this study did not identify significant relationships between risk factors and HPV genotyping in cervical cancer patients. Further research is warranted to explore deeper into the complex interplay between these variables and their potential impact on disease progression. Understanding these nuances can contribute to more personalized approaches to cervical cancer management and prevention.

Keywords: Cervical cancer, HPV genotypes, Risk Factors, Indonesia

INTRODUCTION

Cervical cancer stands as a significant global health issue, ranking as the fourth most prevalent malignancy among women worldwide. According to data from the World Health Organization (WHO) in 2020, approximately 604,000 new cases and 342,000 deaths from cervical cancer were reported, with approximately 90% occurring in low-middle-income countries (World Health Organization, 2022). The global incidence ranges from 75 to 10 cases per 100,000 women (World Health Organization, 2020). Indonesia, as of 2012 data, recorded 20,928 cases of cervical cancer with 9,498 associated deaths (World Health Organization, 2022). World Health Organization (WHO) merekomendasikan tes DNA-HPV sebagai metode skrining yang utama pada tahun 2021(World Health Organization, 2021),

Cervical cancer is preventable, with Human Papillomavirus (HPV) infection being a crucial etiological factor. HPV is present in over 95% of cervical cancer lesions. While there's no direct treatment for the virus, some topical microbicides have shown intrinsic antiviral activity (Calagna et al., 2020). Although most HPV infections are asymptomatic and can resolve on their own, persistent HPV infection poses a risk of developing into precancerous lesions, ultimately leading to cervical cancer (Capra et al., 2017). High-risk HPV types, notably HPV 16 and 18, are responsible for low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) in the cervix. Timely identification and treatment of precancerous lesions can prevent progression (Ministry of Health Republic of Indonesia, 2018). Vaccination, protecting individuals from HPV infection, has demonstrated success in reducing cervical cancer incidence in developed countries alongside regular screening for adult women. However, low-middle-income countries often face limitations in preventive facilities and access, leading to advanced-stage diagnoses (World Health Organization, 2022), as observed in Indonesia, where approximately 66.4% of patients are diagnosed at stages IIB-IVB (Ministry of Health Republic of Indonesia, 2018).

HPV belongs to the Papillomaviridae family, comprising over 200 genotypes. HPV infects the squamous epithelium of the skin and mucous membranes, categorizing it into cutaneous and mucosal types. In terms of cancer and pre-cancerous lesions, HPV is classified into high-risk types associated with malignancy and low-risk types linked to benign lesions (Burd, 2003).

HPV infection is one of the most common sexually transmitted infections worldwide, affecting both men and women. Global genital HPV infection prevalence ranges from 3.5% to 45% in men

and 2% to 44% in women, with similar transmission rates (Kombe Kombe et al., 2020). Most HPV infections in men are asymptomatic and resolve spontaneously, often causing no symptoms. Genital warts are the primary clinical manifestation of symptomatic HPV infection in men, typically benign. In women, while many acquire cervical HPV infections, most do not progress to cervical cancer (Bosco et al., 2021). The integration of HPV into the cell genome is a key factor in cervical cancer development. HPV symptoms may not appear until months or years after infection, making detection challenging until genital warts or cancerous lesions emerge, particularly in women (Hu et al., 2015).

Efforts to eliminate cervical cancer include the WHO's 90-70-90 target for 2030, which aims for 90% of young girls to receive full vaccination at age 15, 70% of women to undergo screening at 35 and 45 years, and 90% of women with cervical cancer to receive management, including recovery from pre-cancerous lesions and treatment for invasive cancer cases (World Health Organization, 2020). Indonesia has responded by planning an HPV vaccination program for female teenagers as part of its national vaccination initiatives. However, this program has yet to encompass the adult female population. To align with the government's goals of developing domestic diagnostic tools and expanding screening reach, it is crucial to create cost-effective, sensitive, and specific diagnostic reagents tailored to the high-risk HPV genotypes commonly found in the Indonesian population. This preliminary study aims to correlate risk factors in to HPV genotypes among women in Indonesia.

MATERIAL AND METHOD/ METHODOLOGY

Ethical Clearance

This study was approved by the ethical clearance committee of Faculty of Medicine, Universitas Indonesia, with ethical clearance number of KET-1262/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from subjects before enrolment.

Study Design and Population

This is a cross-sectional study, observing the relationship between risk factors and HPV genotyping among women in Indonesia. The study was conducted in 2022 in Cipto mangun kusumo National Hospital, Jakarta with the targeted participants of women aged 18-65 years old.

Only women who have signed the informed consent were included in this study. Women who have had a prior HPV vaccination or a treatment related to cervical cancer were excluded from this study.

Data Collection

Forty-one participants were recruited consecutively according to inclusion and exclution criterias. Questionnares were subjected to the participants, containing detailed questions related to marriage status, smoking, and parity status. For HPV genotyping, cervical swab was collected in thin prep container and kept in 4C fridge for genotyping analysis.

HPV Genotyping

DNA Extraction was subjected to cervical swab using QIAamp® DNA Blood mini kit (Qiagen, cat. 51104) according to the manufacture's protocol. Briefly, sample in pellet resuspension was added to mixture of Qiagen Protease (Proteinase K) and Buffer AL. After 10 min and 56°C incubation, ethanol 96-100% was added. The mixture was then transferred to the QIAamp Mini Spin Column and centrifuged at 6000 x g for 1 min. Buffer AW2 and AE were added separately after serial centrifugation at different speeds and time. The extracted DNA was then amplified, and the HPV was genotyped using reverse dot blot "flow-through" hybridization method with GeneFlow Human papillomavirus (HPV) array test kit (cat. 92007). This method can detect different high-risk HPV types, including 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 81 and 82; and HPV low risk types, including 6, 11, 26, 40, 42, 43, 44, 54, 55, 57, 61, 70, 71, 72, and 84.

Statistical Analysis

The data were subjected to analysis using Microsoft Excel 2018 (version 16.16.14). Categorical variables were summarized by presenting absolute values and percentages. For testing the correlation of risk factors and HPV genotyping, Chi-square or Fisher test were used accordingly. All statistical analyses were carried out utilizing Graph Pad version 9.0.0. A p-value (two-tailed) less than 0.05 was considered statistically significant.

RESULTS

This study highlights the characteristics of women with cervical cancer and correlates those characteristics to HPV genotyping. These findings illuminate the multifaceted nature of patient characteristics in the study, underscoring the endeavor to explore the correlations between risk factors and HPV genotyping in cervical cancer among Indonesian patients.

Characteristics of participants

The study emphasizes the significance of patient age. The age distribution varied, with a minor proportion in the 25-34 age group, while the majority were aged 35 or older. Age at marriage emerged as a noteworthy factor. Roughly 44.4% of patients were married before the age of 20, while about 55.6% married at an age older than 20. There was substantial variation in the age at which patients experienced their first pregnancy. Approximately 25% of patients had their initial pregnancy before the age of 20, and 75% experienced it between the ages of 20 and 35. Differences in the number of parities among patients were observed, with 11.1% categorized as nulliparous (never having given birth) and 88.9% classified as multiparous (having given birth more than once). Smoking habits exhibited significant variability among patients, with 10.3% identified as active smokers and 89.7% as non-smokers (Table 1).

Diagnostic data reflected the severity of cervical cancer in the patients. A minority received a pre-cancer diagnosis, while 50% were at stage 2, 23.1% at stage 3, and 3.84% at stage 4, indicating differing levels of severity. The patterns of contraceptive use were diverse, with 33.3% of patients not using contraception and 66.7% using contraceptive methods. The study unveiled a diversity of HPV infections. Around 53.7% had no detectable high-risk or low-risk HPV types, 43% had high-risk HPV types, and 2.4% had low-risk HPV types. Various high-risk HPV types were identified, with HPV type 16 in some patients and HPV type 18 in others, among others. Low-risk HPV type 26 was detected in approximately 5.3% of patients. Coinfections were found in three women, possesing HPV type 16 and 52; 18, 66 and 68; and 26 and 84.

Relationship between risk factors and HPV genotyping

The relationship between risk factors and HPV genotyping was analysed using Chi-square or Fisher test. All categories were adjusted according to the criteria of statistical analysis. Most

participants possed high-risk HPV were in the groups of >45 years of age, >20 years at the time of marriage and pregnancy, multiparous, not being a smoker, and using contraceptions. However, we did not observe any significant relationships between those factors and HPV genotyping (Table 2).

DISCUSSION

This study highlights the importance of internal and external factors to the types of HPV infected women. However, no significant association was found in every factor with high-risk HPV. Surprisingly, we found that HPV type 52 dominated the HPV types found in women with cervical cancer.

Most of participants who were infected with high-risk HPV were older than 45 years old. Age of patients is a critical factor in understanding the dynamics and persistence of HPV infection. A study shows that high-risk HPV infection will develop into cervical cancer mostly at the age of 40 years old (Burger et al., 2017). Young aged women have a higher likelihood of clearing HPV infections spontaneously, while older women may experience persistent infections (Huber et al., 2021). Supporting our results, a study found that HPV type 18 and 45 are more prevalent in young women (Kong et al., 2019), highlighting the importance of examining age distribution among HPV genotyping data to enhance our understanding about age-related patterns in HPV infections.

Contrary to our results, several studies show the increasing number of cervical cancer in women age 20 – 29 years old in UK annually up to 10% (Patel et al., 2012), under 30 years old in Taiwan (Lau et al., 2009) and younger than 30 years old in China (Li et al., 2013).

Age of marriage and pregnancy is closely related to high-risk HPV infection that leads to cervical cancer. Early exposure to HPV is mostly through sexual activity and increases the risk of infection, especially to HPV type 16, whereas multiple sexual partners can increase the risk of HPV type 18 infection (Itarat et al., 2019). However, we did not analyse this factor. The age of pregnancy has been linked to HPV infection. A study in China shows a significant increase in susceptibility of HPV infection in pregnant women older than 35 years (Luo et al., 2021). In agreement with our results, HPV type 52 is the most prevalent HPV type found in these group age pregnant women (Luo et al., 2021).

Smoking is believed to be responsible for the development of cervical cancer. Tobacco increases HPV replication, promotes E6 and E7 oncoprotein expressions, decreases the ability of immune systems to clear the HPV infection and also promotes DNA damage due to HPV infection (Aguayo et al., 2020). Moreover, prolonged smoking exposure is thought to be promote a persistence HPV infection (Ma* et al., 2023), leading to the development of cervical cancer.

The use of hormonal contraception has been linked to the development of cervical cancer. However, this has become a controversial topic due to inconsistency in research. We did not find any significant correlation between the use of contraception and HPV genotyping. Similar to our study, a literature study found no significant correlation between the use of oral contraception and the risk of cervical cancer (Gadducci et al., 2020). A study in Finland also showed that there were no association between the methods of contraception and high-risk HPV infection (Bergqvist et al., 2021). Our results suggest that the use of contraception is not likely to related to high-risk HPV infection, however, more further studies about the type and the length of contraception used, especially in younger women are needed to reveal the trend of increasing incindence of cervical cancer in this age group.

CONCLUSION

The type of high-risk HPV varies among women with cervical cancer with HPV type 52 being the major type of HPV infection. Risk factors are also varies among women with cervical cancer and it is unlikely associated with HPV genotyping. Further studies on various risk factors and HPV genotyping are needed, especially in young aged women to targetting an alternative preventive strategy in cervical cancer.

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Table 1(on next page)

Characteristics of participants

Characteristics	Total	Percentage
Age (years)		
25-34	3	7.3
35-44	11	26.8
45-50	11	26.8
>50	16	39
Age at marriage		
<20	12	44.4
>20	15	55.6
Age at pregnancy		
<20	7	25.0
20-35	21	75.0
Parity number		
Nulliparous	3	11.1
Multiparous	24	88.9
Smoking		
Yes	3	10.3
No	26	89.7
Cancer stadium		
Pre-Cancer	3	11.5
Stadium 1	3	11.5
Stadium 2	13	50.0
Stadium 3	6	23.1
Stadium 4	1	3.8
Contraception		

Yes	10	66.7
No	5	33.3
HPV genotyping		
No HPV	22	53.7
High-risk HPV	18	43.9
Low-risk HPV	1	2.4
HPV type		
16	3	15.8
18	4	21.1
26	1	5.3
35	1	5.3
45	1	5.3
52	5	26.3
58	1	5.3
59	2	10.5
73	1	5.3

1

2

Table 2(on next page)

Association of risk factors and HPV genotyping in women with cervical cancer

1

Risk Factors	No HPV/low-risk HPV	High-risk HPV	p value
Age (years)			
<45	6	5	0.373
>=45	8	13	
Age at marriage			
<20	1	7	1
>20	2	9	
Age at pregnancy			
<20	0	5	0.539
20-35	3	12	
Parity number			
Nulliparous	1	0	0.143
Multiparous	1	12	
Smoking			
Yes	0	3	1
No	3	14	
Contraception			
Yes	1	5	1
No	0	4	

2

3

4

5

Risk factors and HPV genotypes: investigating their interplay in cervical cancer

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Abstract

Cervical cancer remains a significant global health challenge, primarily associated with Human Papillomavirus (HPV) infection. This study examines the relationship between various risk factors and HPV types in cervical cancer patients to understand how patient traits may influence disease progression. Women with cervical cancer were enrolled in this cross-sectional study, with cervical swabs collected for HPV genotyping. Risk factors such as age, age at marriage, age at first pregnancy, parity, smoking, contraceptive history, and cancer stage were assessed through a questionnaire. Statistical analysis was performed using the Chi-square or Fisher test with a significance level of $p<0.05$. The findings revealed that HPV type 52 was the most common high-risk type, followed by HPV types 16 and 18. However, no significant associations were found between patient characteristics and HPV genotypes ($p>0.05$). In conclusion, despite variations in patient traits, including reproductive history and lifestyle factors, these did not correlate significantly with specific HPV types. Further research is needed to explore the complex interactions between these factors and their potential impact on cervical cancer progression, which could enhance personalized management and prevention strategies.

Keywords: Cervical cancer, HPV genotypes, Risk Factors, Indonesia

INTRODUCTION

Cervical cancer stands as a significant global health issue, ranking as the fourth most prevalent malignancy among women worldwide. According to data from the World Health Organization (WHO) in 2020, approximately 604,000 new cases and 342,000 deaths from cervical cancer were reported, with approximately 90% occurring in low-middle-income countries (World Health Organization, 2022). The

global incidence ranges from 75 to 10 cases per 100,000 women (World Health Organization, 2020). Indonesia, as of 2012 data, recorded 20,928 cases of cervical cancer with 9,498 associated deaths (World Health Organization, 2022). World Health Organization (WHO) merekomendasikan tes DNA-HPV sebagai metode skrining yang utama pada tahun 2021(World Health Organization, 2021),

Cervical cancer is preventable, with Human Papillomavirus (HPV) infection being a crucial etiological factor. HPV is present in over 95% of cervical cancer lesions. While there's no direct treatment for the virus, some topical microbicides have shown intrinsic antiviral activity (Calagna et al., 2020; Sutanto&Hartanti, 2020). Although most HPV infections are asymptomatic and can resolve on their own, persistent HPV infection poses a risk of developing into precancerous lesions, ultimately leading to cervical cancer (Capra et al., 2017; Hartanti et al., 2020; Kogoya et al., 2023). High-risk HPV types, notably HPV 16 and 18, are responsible for low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) in the cervix. Timely identification and treatment of precancerous lesions can prevent progression (Ministry of Health Republic of Indonesia, 2018). Vaccination, protecting individuals from HPV infection, has demonstrated success in reducing cervical cancer incidence in developed countries alongside regular screening for adult women. However, low-middle-income countries often face limitations in preventive facilities and access, leading to advanced-stage diagnoses (World Health Organization, 2022), as observed in Indonesia, where approximately 66.4% of patients are diagnosed at stages IIB-IVB (Ministry of Health Republic of Indonesia, 2018).

HPV belongs to the Papillomaviridae family, comprising over 200 genotypes. HPV infects the squamous epithelium of the skin and mucous membranes, categorizing it into cutaneous and mucosal types. In terms of cancer and pre-cancerous lesions, HPV is classified into high-risk types associated with malignancy and low-risk types linked to benign lesions (Burd, 2003).

HPV infection is one of the most common sexually transmitted infections worldwide, affecting both men and women. Global genital HPV infection prevalence ranges from 3.5% to 45% in men and 2% to 44% in women, with similar transmission rates (Kombe Kombe et al., 2020). Most HPV infections in men are asymptomatic and resolve spontaneously, often causing no symptoms. Genital warts are the primary clinical manifestation of symptomatic HPV infection in men, typically benign. In women, while many acquire cervical HPV infections, most do not progress to cervical cancer (Bosco et al., 2021). The integration of HPV into the cell genome is a key factor in cervical cancer development. HPV symptoms may not appear until months or years after infection, making detection challenging until genital warts or cancerous lesions emerge, particularly in women (Hu et al., 2015).

Efforts to eliminate cervical cancer include the WHO's 90-70-90 target for 2030, which aims for 90% of young girls to receive full vaccination at age 15, 70% of women to undergo screening at 35 and 45 years, and 90% of women with cervical cancer to receive management, including recovery from pre-cancerous lesions and treatment for invasive cancer cases (World Health Organization, 2020). Indonesia has responded by planning an HPV vaccination program for female teenagers as part of its national vaccination initiatives. However, this program has yet to encompass the adult female population. To align with the government's goals of developing domestic diagnostic tools and expanding screening reach, it is crucial to create cost-effective, sensitive, and specific diagnostic reagents tailored to the high-risk HPV genotypes commonly found in the Indonesian population. This preliminary study aims to correlate risk factors in to HPV genotypes among women in Indonesia.

MATERIAL AND METHOD/ METHODOLOGY

Ethical Clearance

This study was approved by the ethical clearance committee of Faculty of Medicine, Universitas Indonesia, with ethical clearance number of KET-1262/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from subjects before enrolment.

Study Design and Population

This is a cross-sectional study, observing the relationship between risk factors and HPV genotyping among women in Indonesia. The study was conducted in 2022 in Cipto mangun kusumo National Hospital, Jakarta with the targeted participants of women aged 18-65 years old. Only women who have signed the informed consent were included in this study. Women who have had a prior HPV vaccination or a treatment related to cervical cancer were excluded from this study.

Data Collection

Forty-one participants were recruited consecutively according to inclusion and exclution criterias. Questionnares were subjected to the participants, containing detailed questions related to marriage status, smoking, and parity status. For HPV genotyping, cervical swab was collected in thin prep container and kept in 4C fridge for genotyping analysis.

HPV Genotyping

DNA Extraction was subjected to cervical swab using QIAamp® DNA Blood mini kit (Qiagen, cat. 51104) according to the manufacture's protocol. Briefly, sample in pellet resuspension was added to mixture of Qiagen Protease (Proteinase K) and Buffer AL. After 10 min and 56°C incubation, ethanol 96-100% was added. The mixture was then transferred to the QIAamp Mini Spin Column and centrifuged at 6000 x g for 1 min. Buffer AW2 and AE were added separately after serial centrifugation at different speeds and time. The extracted DNA was then amplified, and the HPV was genotyped using reverse dot blot "flow-through" hybridization method with GeneFlow Human papillomavirus (HPV) array test kit (cat. 92007). This method can detect different high-risk HPV types, including 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 81 and 82; and HPV low risk types, including 6, 11, 26, 40, 42, 43, 44, 54, 55, 57, 61, 70, 71, 72, and 84.

Statistical Analysis

The data were subjected to analysis using Microsoft Excel 2018 (version 16.16.14). Categorical variables were summarized by presenting absolute values and percentages. For testing the correlation of risk factors and HPV genotyping, Chi-square or Fisher test were used accordingly. All statistical analyses were carried out utilizing Graph Pad version 9.0.0. A p-value (two-tailed) less than 0.05 was considered statistically significant.

RESULTS

This study highlights the characteristics of women with cervical cancer and correlates those characteristics to HPV genotyping. These findings illuminate the multifaceted nature of patient characteristics in the study, underscoring the endeavor to explore the correlations between risk factors and HPV genotyping in cervical cancer among Indonesian patients.

Characteristics of participants

The study emphasizes the significance of patient age. The age distribution varied, with a minor proportion in the 25-34 age group, while the majority were aged 35 or older. Age at marriage emerged as a noteworthy factor. Roughly 44.4% of patients were married before the age of 20, while about 55.6% married at an age older than 20. There was substantial variation in the age at which patients experienced their first pregnancy. Approximately 25% of patients had their initial pregnancy before the age of 20, and 75% experienced it between the ages of 20 and 35. Differences in the number of parities among patients were observed, with 11.1% categorized as nulliparous (never having given birth) and 88.9% classified as multiparous (having

given birth more than once). Smoking habits exhibited significant variability among patients, with 10.3% identified as active smokers and 89.7% as non-smokers (Table 1).

Table 1. Characteristics of Participants

Characteristics	Total	Percentage
Age (years)		
25-34	13	18.3
35-44	20	28.2
45-50	17	23.9
>50	121	29.6
Age at marriage		
<20	18	25.4
>20	52	73.2
Single	1	1.4
Age at pregnancy		
<20	9	12.7
20-35	55	77.5
>35	2	2.8
Single	5	7.0
Parity number		
Nulliparous	7	9.9
Multiparous	64	90.1
Smoking		
Yes	4	5.6
No	67	94.4
Cancer stadium		
Pre-Cancer	11	15.5
Stadium 1	7	9.9
Stadium 2	20	28.2
Stadium 3	7	9.9
Stadium 4	1	1.4
No Cancer	25	35.2
Contraception		
Yes	28	39.4
No	43	60.6

HPV genotyping		
No HPV	29	40.8
High-risk HPV	40	56.3
Low-risk HPV	2	2.8
HPV type		
16	8	11.03
18	8	11.03
31	1	1.04
33	2	2.08
39	1	1.04
26	1	5.3
35	1	5.3
45	2	5.3
52	8	26.3
58	1	5.3
59	2	10.5
73	1	5.3
16/31	1	1.04
16/52	1	1.04
18/66/68	1	1.04
81	1	1.04

Diagnostic data reflected the severity of cervical cancer in the patients. A minority received a pre-cancer diagnosis, while 50% were at stage 2, 23.1% at stage 3, and 3.84% at stage 4, indicating differing levels of severity. The patterns of contraceptive use were diverse, with 33.3% of patients not using contraception and 66.7% using contraceptive methods. The study unveiled a diversity of HPV infections. Around 53.7% had no detectable high-risk or low-risk HPV types, 43% had high-risk HPV types, and 2.4% had low-risk HPV types. Various high-risk HPV types were identified, with HPV type 16 in some patients and HPV type 18 in others, among others. Low-risk HPV type 26 was detected in approximately 5.3% of patients. Coinfections were found in three women, possesing HPV type 16 and 52; 18, 66 and 68; and 26 and 84.

Relationship between risk factors and HPV genotyping

The relationship between risk factors and HPV genotyping was analysed using Chi-square or Fisher test. All categories were adjusted according to the criteria of statistical analysis. Most participants possed high-risk HPV were in the groups of 45-50 years of age, >20 years at the time of marriage and pregnancy, multiparous, not being a smoker, and did not use contraceptions. However, we did not observe any significant relationships between those factors and HPV genotyping (Table 2).

Table 2. Association of risk factors and HPV genotyping in women with cervical cancer

Risk Factors	No HPV/low-risk HPV	High-risk HPV	p value
Age (years)			
25-34	8	5	
35-44	8	12	
45-50	9	8	
>50	6	15	0.227[$]
Age at marriage			
<20	2	16	0.002
>20	29	23	
Single		1*	
Parity number*			
Nulliparous	3	4	0.999
Multiparous	28	36	
Contraception			
Yes	11	17	0.628
No	20	23	

$ Chi-square was used for statistics analysis
* One subject was identified as single

DISCUSSION

This study highlights the importance of internal and external factors to the types of HPV infected women. However, no significant association was found in every factor with high-risk HPV. Surprisingly, we found that HPV type 52 dominated the HPV types found in women with cervical cancer.

Most of participants who were infected with high-risk HPV were older than 45 years old but younger than 50 years. Age of patients is a critical factor in understanding the dynamics and persistence of HPV infection. A study shows that high-risk HPV infection will develop into cervical cancer mostly at the age of 40 years old (Burger et al., 2017). Young aged women have a higher likelihood of clearing HPV infections spontaneously, while older women may experience persistent infections (Huber et al., 2021). Supporting our results, a study found that HPV type 18 and 45 are more prevalent in young women (Kong et al., 2019), highlighting the importance of examining age distribution among HPV genotyping data to enhance our understanding about age-related patterns in HPV infections.

Contrary to our results, several studies show the increasing number of cervical cancer in women age 20 – 29 years old in UK annually up to 10% (Patel et al., 2012), under 30 years old in Taiwan (Lau et al., 2009) and younger than 30 years old in China (Li et al., 2013).

Age of marriage and pregnancy is closely related to high-risk HPV infection that leads to cervical cancer. Early exposure to HPV is mostly through sexual activity and increases the risk of infection, especially to HPV type 16, whereas multiple sexual partners can increase the risk of HPV type 18 infection (Itarat et al., 2019). However, we did not analyse this factor. The age of pregnancy has been linked to HPV infection. A study in China shows a significant increase in susceptibility of HPV infection in pregnant

women older than 35 years (Luo et al., 2021). In agreement with our results, HPV type 52 is the most prevalent HPV type found in these group age pregnant women (Luo et al., 2021).

Smoking is believed to be responsible for the development of cervical cancer. Tobacco increases HPV replication, promotes E6 and E7 oncoprotein expressions, decreases the ability of immune systems to clear the HPV infection and also promotes DNA damage due to HPV infection (Aguayo et al., 2020). Moreover, prolonged smoking exposure is thought to be promote a persistence HPV infection (Ma* et al., 2023), leading to the development of cervical cancer.

The use of hormonal contraception has been linked to the development of cervical cancer. However, this has become a controversial topic due to inconsistency in research. We did not find any significant correlation between the use of contraception and HPV genotyping. Similar to our study, a literature study found no significant correlation between the use of oral contraception and the risk of cervical cancer (Gadducci et al., 2020). A study in Finland also showed that there were no association between the methods of contraception and high-risk HPV infection (Bergqvist et al., 2021). Our results suggest that the use of contraception is not likely to related to high-risk HPV infection, however, more further studies about the type and the length of contraception used, especially in younger women are needed to reveal the trend of increasing incindence of cervical cancer in this age group.

CONCLUSION

The type of high-risk HPV varies among women with cervical cancer with HPV type 52 being the major type of HPV infection. Risk factors are also varies among women with cervical cancer and it is unlikely associated with HPV genotyping. Further studies on various risk factors and HPV genotyping are needed, especially in young aged women to targetting an alternative preventive strategy in cervical cancer.

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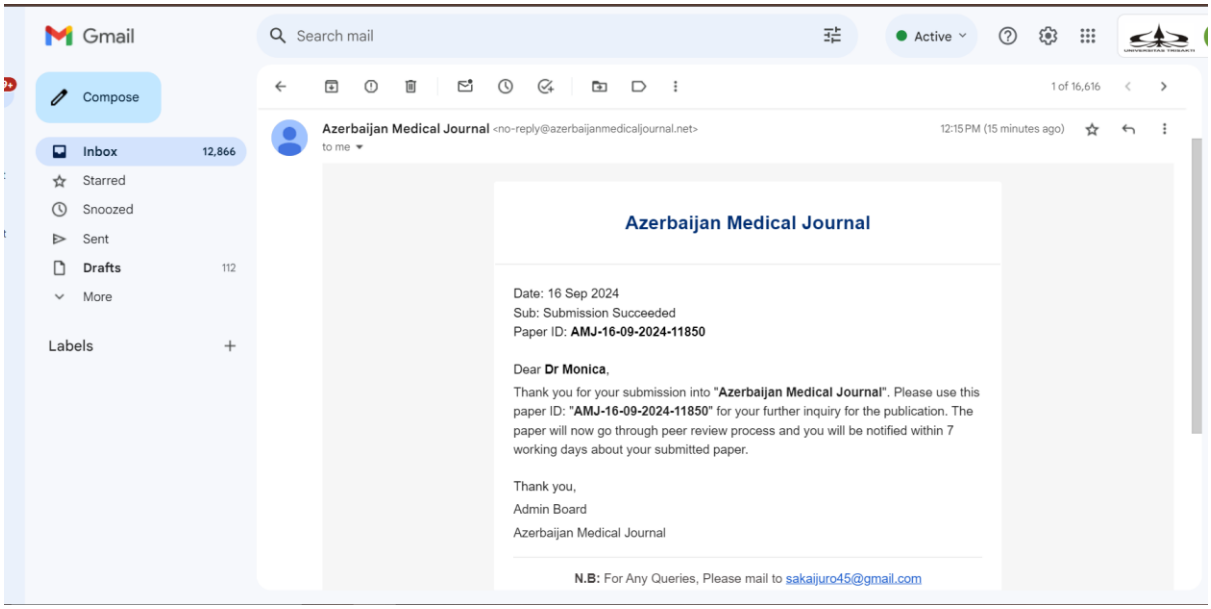
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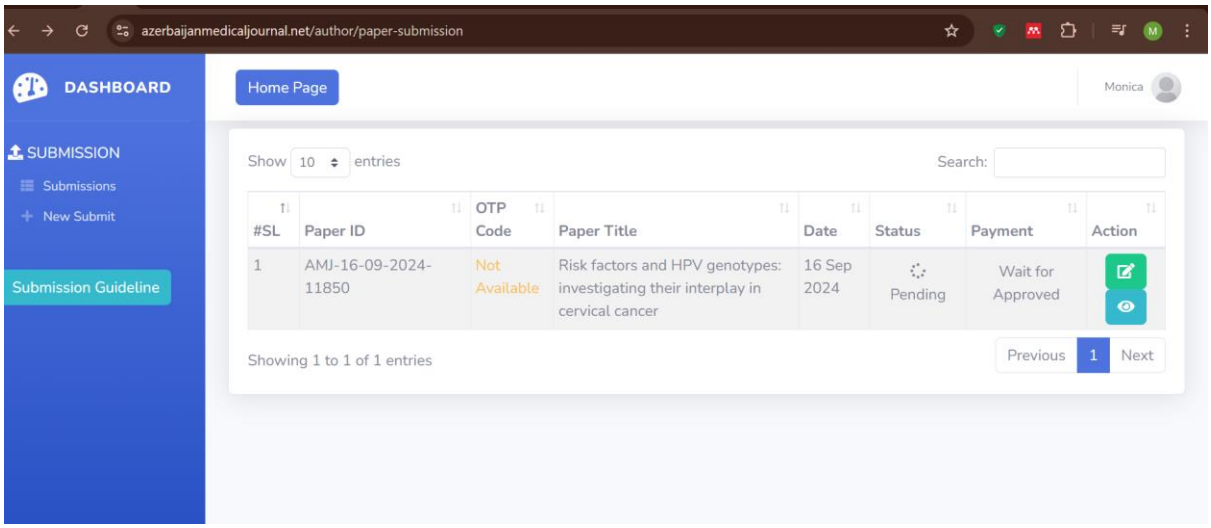
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Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi

UNIVERSITAS TRISAKTI

Kampus Merdeka INDONESIA JAYA

Perancangan alat deteksi genotyping HPV berbasis multiplex recombinase polymerase amplification dan nucleic acid lateral flow immunoassay (mRPA- NALFIA) sebagai alternatif metode PCR skrining kanker serviks yang mudah dan murah di fasilitas kesehatan primer

Tim Peneliti:

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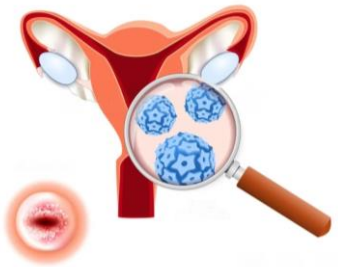
- **drh. Muhammad Ibrahim Desem, S.K.H., M.Si**
- **Dr. Sunarno, M.Si.Med**
- **Dr. dr Christina Safira Whinie Lestari, M.Kes**



Tahun 2023

Universitas Trisakti

Latar Belakang

IVA

Pap Smear

DNA HPV

Biaya pengobatan kanker serviks tertinggi dibanding dengan kanker lain, mencapai skitar 400 juta.

Kanker serviks dapat dicegah dengan skrining

Pap Smear dan IVA merupakan metode skrining, namun sensitivitas dan spesifisitas yang relatif rendah

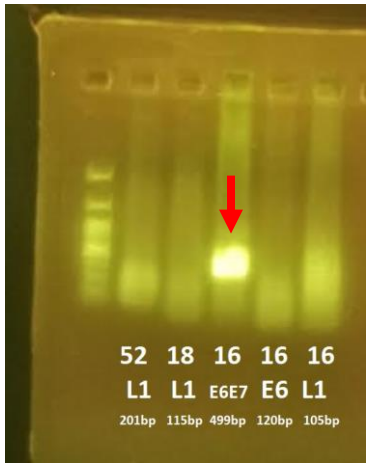
WHO menyarankan pemeriksaan DNA HPV sebagai bagian dari skrining, namun merlukan mesin PCR yang mahal harganya

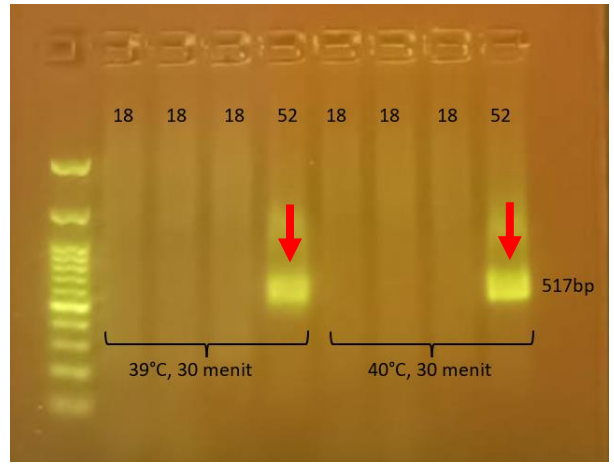
Multiple Recombinase Polymerase Amplification adalah amplification merupakan uji isotermal dengan suhu tunggal 37-42°C sehingga dipercaya dapat menggantikan metode PCR sebagai point of care test.

Hasil amplifikasi dapat divisualisasikan dengan perangkat elektroforesis maupun metode nucleic acid lateral flow immunoassay (NALFIA).

Metode dan Hasil

No.	Aktivitas	Bukti Luaran	Target Indikator Capaian	Realisasi
1	Desain algoritma dan seleksi primer mRPA	Primer yang siap digunakan	Tersedia	100 %
2	Modifikasi protokol PCR dan optimasi kondisi reaksi mRPA	Protokol PCR dan reaksi mRPA yang siap digunakan	Tersedia	100 %
3	Evaluasi primer mRPA dengan PCR dan persiapan template DNA	Primer mRPA dan template DNA yang siap digunakan	Tersedia	100 %
4	Modifikasi dan uji protokol PCR dan mRPA dengan primer berlabel	PCR dan mRPA dengan primer berlabel memiliki hasil yang sama dengan primer tanpa label	Tersedia	97 %





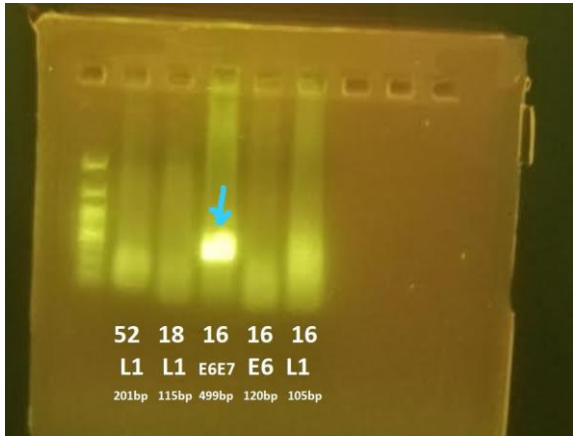
Luaran

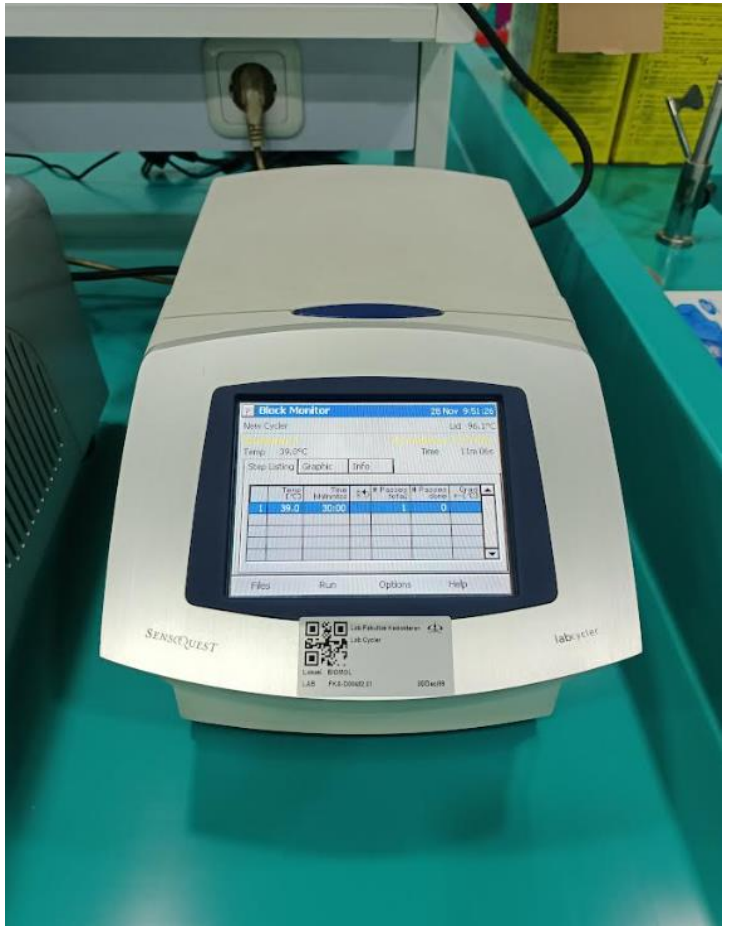
Aktivitas	Bukti Luaran	Target Indikator Capaian	Realisasi
Pembuatan laporan lengkap dan luaran	Publikasi di jurnal internasional terindex SCOPUS Q1 PeerJ	Accepted	80 % Submitted
	Hak Cipta buku saku mRPA-NALFIA	Sertifikat terbit	100 %

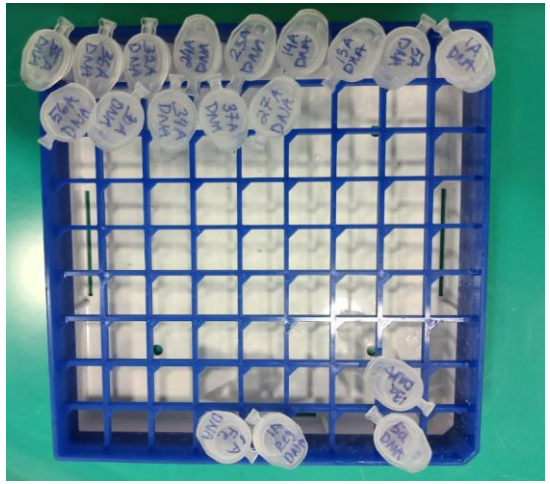
Kesimpulan dan Saran

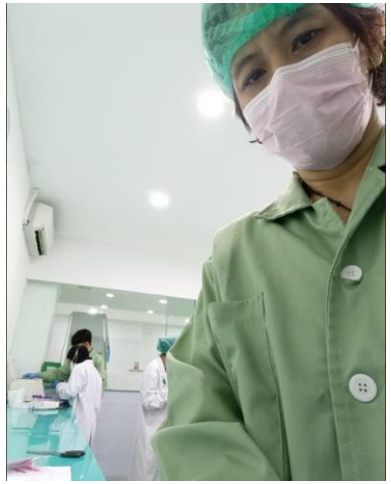
- Pada **tahun pertama** luaran telah tercapai sebesar **98 %**
- Protokol RPA untuk tiga tipe HPV yang optimal pada suhu 39°C selama 30 menit dengan finalisasi optimasi akhir pasangan primer HPV tipe 18.
- Walaupun tahap pada tahun pertama selesai, namun diperlukan **kelanjutan penelitian pada tahap kedua**, yaitu dengan membuat visualisasi dari mRPA dengan NALFIA (nucleic acid lateral flow immuno assay) agar memudahkan dan mempercepat visualisasi hasil mRPA menuju **komersialisasi invensi**
- Hasil akhir yang diharapkan pada **tahun kedua** adalah
  - **Purwarupa** alat skrining kanker serviks berupa deteksi HPV tipe 16, 18 dan 52 yang dapat digunakan pada puskesmas.
  - **Pendaftaran hak paten sederhana**
  - **Monograf** berISBN

Foto Kegiatan Penelitian









SURAT PERNYATAAN TANGGUNG JAWAB BELANJA

Yang bertanda tangan di bawah ini :

Nama : Dr Dr RADITYA WRATSANGKA Sp.OG

Alamat : JL. KEMANGGISAN RAYA NO. 110 RT. 001 / RW. 019, KEL. KEMANGGISAN KEC. PALMER

berdasarkan Surat Keputusan Nomor 179/E5/PG.02.00/PL/2023 dan Perjanjian / Kontrak Nomor 1440/LL3/AL.04/2023; 705/A/LPPM/USAKTI/VII/2023 mendapatkan Anggaran Penelitian Perancangan alat deteksi genotyping HPV berbasis multiplex recombinase polymerase amplification dan nucleic acid lateral flow immunoassay (mRPA-NALFIA) sebagai alternatif metode PCR skrining kanker serviks yang mudah dan murah di fasilitas kesehatan primer Sebesar 221,100,000

Dengan ini menyatakan bahwa :

1. Biaya kegiatan Penelitian di bawah ini meliputi :

No	Uraian	Jumlah
01	**Bahan** Bahan penelitian (habis pakai) (tips mikropipet, microtubes, kit isolasi DNA, kit PCR, primer tanpa label, primer dengan label, agarose, antibodi, dan twistAMP, HPV genotyping)	221,100,000
02	**Pengumpulan Data**	0
03	**Analisis Data(Termasuk Sewa Peralatan**	0
04	**Pelaporan, Luaran Wajib dan Luaran Tambahan**	0
05	**Lain-lain**	0
	Jumlah	221,100,000

2. Jumlah uang tersebut pada angka 1, benar-benar dikeluarkan untuk pelaksanaan kegiatan Penelitian dimaksud.

Demikian surat pernyataan ini dibuat dengan sebenarnya.

Jakarta, 30-11-2023

Ketua,

(Dr Dr RADITYA WRATSANGKA Sp.OG)

NIP/NIK 3173072705620002